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The effectiveness and cost effectiveness of immunoglobulin replacement therapy for primary immunodeficiency and chronic lymphocytic leukaemia: a systematic review and economic evaluation.

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West Midlands Health Technology Assessment Group

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The effectiveness and cost-effectiveness of immunoglobulin replacement therapy for primary immunodeficiency and chronic lymphocytic leukaemia: a systematic review and economic evaluation

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WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION (WMHTAC)

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

CONTRIBUTIONS OF AUTHORS

Zulian Liu was the main reviewer. She was responsible for the day-to-day management of the report; undertook all searches for effectiveness assessment; designed the protocol, designed and piloted study inclusion and data extraction; undertook assessment of study eligibility, validity and collated data; and wrote the report except the health economic evaluation section.

Esther Albon assisted in the development of the protocol; checked the selection of the studies and part of the data extraction.

Chris Hyde was the project manager and took overall responsibility for the report. He searched, identified and selected the studies for cost-effectiveness assessment and wrote the section; advised on protocol development and all aspects of the report; he checked part of the effectiveness data extraction; he directed the report and edited parts of the manuscript.

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GLOSSARY/ABBREVIATIONS AND ACRONYMS

Abbreviation / acronym	Definition
ARIF	Aggressive Research Intelligence Facility
CLL	chronic lymphocytic leukaemia
CVID	common variable immunodeficiency
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
Ig or IG	Immunoglobulin
IgAD	selective IgA deficiency
IgRT	Immunoglobulin Replacement Therapy
IM	intramuscular injection
IMIg	intramuscular immunoglobulin
ITT	intention to treat
IV	intravenous infusion
IVIg	intravenous immunoglobulin
IVIG-C	intravenous immunoglobulin preparation Gamunex™
IVIG-N	intravenous immunoglobulin preparation, nanofiltered
IVIG-SD	intravenous immunoglobulin preparation, solvent detergent treated
PCT	Primary Care Trust
PID	primary immunodeficiencies
QoL	quality of life
RCT	randomized controlled trial
REP	Regional Evaluation Panel
SCID	severe combined immune deficiency
SD	standard deviation
SE	standard error
SC	Subcutaneous injection/infusion
SCIg	subcutaneous immunoglobulin
WMHTAC	West Midlands Health Technology Assessment Collaboration
XLA	X-linked Agammaglobulinemia

Executive Summary

Background

Immunoglobulin replacement therapy (IgRT) has been used to treat patients with immunoglobulin deficiency for over five decades. It is however high cost, so inevitably questions of cost-effectiveness have been raised.

Aim

To assess the effectiveness and cost-effectiveness of IgRT for patients with primary immunoglobulin deficiency (PID) and immunoglobulin deficiency secondary to chronic lymphocytic leukemia (CLL).

Effectiveness – method

A systematic review was performed. The Cochrane Library (2005 issue 2 for CDSR, DARE, CENTRAL, HTA, and NHSEED), MEDLINE (Ovid) (1966 to 2005 April week 3), EMBASE (Ovid) (1980 to 2005 week 17), and CINAHL (Ovid) (1982 to 2005 April week 4) were searched in April and May 2005 using relevant key words and search filters. Randomised controlled trials (RCTs), quasi-randomised controlled trials (q-RCT) and cross-over trials, comparing IgRT with placebo or no treatment, or comparing dosage, infusion levels, preparation types in patients with PID / CLL were included. There was no restriction on outcomes considered. The main reviewer (ZL) assessed methodological quality and abstracted data, the process being checked by either the second or third reviewers (EA, CH). Analysis was qualitative, conclusions being derived from patterns in the tabulated results. Clinical and methodological heterogeneity precluded meta-analysis.

Effectiveness – general results

17 studies involving PID participants (including 3 parallel and 14 crossover trials) and 5 studies involving CLL patients (including 3 parallel and 2 crossover trials) were included. The sample size of the studies was generally small and the methodological quality of the studies was also generally poor. There were major shortcomings in the design, analysis, and reporting of the

crossover trials. The trials were however often done many years ago when methodological standards were not as clearly defined.

Effectiveness – results for PID

No studies comparing IgRT with placebo or no treatment were identified. Evidence from two old trials showed that administering IgG by the intravenous route (IVIG) is significantly more effective than the intramuscular route (IMIG) in reducing infection or infection-related events. A further small trial showed that the IVIg had more infection episodes (67 vs 45) but less mild and moderate reactions than subcutaneous immunoglobulin (SCIg). Higher doses of IVIG in 3 trials seemed to offer greater reductions in infection. Most of the included studies compared one type of preparation with another, these are described in detail in the main report. Serious adverse events with IgRT were very rare across all the RCTs. Similarly, no evidence of IgRT associated death was found from the identified RCTs.

Effectiveness – results for CLL

IVIg significantly reduced infection events compared to placebo or no treatment, but tended to induce more adverse events. One trial reported patients becoming positive for anti-HCV antibodies while receiving IVIG therapy.

Economic evaluation – method

A systematic review of cost, quality of life and cost-effectiveness studies was conducted. MEDLINE (Ovid) (1966 to July 2005), NHS EED via the Cochrane Library 2005, Issue 2 and OHE HEED July 2005 Issue were searched. Any study with relevant information was included and described. Further economic evaluation focused on the cost-effectiveness of IgRT for PID. Estimates of the effect of IgRT on mortality were sought; the relative costs of SCIg and IVIg in the context of current UK practice were examined; and a Markov model assessing the cost-utility of IgRT relative to no IgRT was designed and run.

Economic evaluation – results for PID

There were no previous health economic evaluations of IgRT relative to no IgRT. The systematic review also revealed there was useful information on costs and the effects of IgRT on health-related quality of life. Two cost-minimisation analyses outside the UK have concluded that SCIg is lower cost than IVIg, and so more cost-effective if the assumption that SCIg and IVIg are equally effective is sound.

The further economic evaluation found evidence that crudely quantifies the effect of IgRT on survival. 10 year survival in a PID group treated with IVIg was 78%; 10 year survival in a cohort treated with relatively low-dose IMIg, soon after it was introduced, was 38%. Investigation of the cost difference between SCIg and IVIg given at home found no evidence for major differences in price or wider cost between the two in the UK at present. The exception is where IVIg infusion is only given in hospital and charges are levied, in which case SCIg at home remains the more cost-effective option. Finally although subject to considerable uncertainty, the health economic model calculated the incremental cost-effectiveness ratio (ICER) to be £30,000 per QALY (UK 2005).

Economic evaluation – results for CLL

The systematic review identified a well conducted health economic model based on the results of one of the RCTs comparing IgRT with placebo in CLL. It calculated the ICER to be approximately $6 million per QALY (US 1989).

Conclusions

IgRT, particularly IVIg and SCIg, is effective in terms of reduction of infection in both PID and CLL. In PID, IgRT appears to be cost-effective, although this assessment depends on evidence on effects on survival and utility that are not derived from RCTs. In contrast, in CLL, IgRT is not cost-effective.

There appear to be no major implications for practice, bar encouraging use of home based IgRT, or unless IgRT is being extensively used in the treatment of patients with CLL. There are implications for research particularly further

development and testing of the new health economic model on IgRT in PID and improving the accuracy of the parameters used in it. Re-running the previously published health economic model on IgRT in CLL, might also be justified, particularly if it focused on cost-utility in groups with high levels of infection.

CONTENTS

1 Introduction

Immunoglobulin replacement therapy (IgRT) is used to treat patients with immunoglobulin deficiency. The efficacy of this therapy has been well established based on both patho-physiological rationale and clinical experience that the therapy for immunoglobulin deficiency syndromes appears to reduce infections, which were the main problems associated with hypogammaglobulinaemia, and can be life saving. [1] Nonetheless, some uncertainty remains about optimum IgRT, particularly route of administration.[2]

IgRT can be administered by three routes: intravenous infusion (IVIg), intramuscular injection (IMIg), and subcutaneous injection (SCIg). IMIG is often poorly tolerated due to pain at injection site and may also be impossible to maintain levels of plasma immunoglobulin sufficient to prevent recurrent infection. Slow administration by subcutaneous route was introduced for those patients poorly compliant with intramuscular injection to avoid local pain; adverse effects of SC are usually mild and local, and the incidence of systemic adverse effects is very rare.[3] Desirable blood IgG level can be achieved by IVIG[2] and SCIG[3]; but long-term intravenous immunoglobulin infusion may be complicated by poor venous access and systemic adverse reactions;[4] also, currently available intravenous preparations differ widely in manufacturing process, methods of viral inactivation and removal and final composition; the impact of these variables on clinical outcomes is still not clear.[5] In 1990's IVIG was more popular in the US, while in other countries patients used SC and IM route. [2,3,6]

It is an overall consensus that high-dose immunoglobulin is superior to lower doses. Self-administration of immunoglobulin at home is preferable for patients as travel to and from hospital and time off school or work are avoided. Home-based SCIG therapy is much simpler than that of intravenous infusion, but intravenous self-infusion at home has also become a realistic alternative to hospitalization.[2]

Home therapy is claimed to offer a saving in the added costs of outpatient

hospitalization and therefore to be more cost-effective.[2] It was reported in 1995 that the costs of immunoglobulin therapy by subcutaneous route cost only about 25-33% of the cost of the therapy by intravenous route.[6] However, there have been some major recent increases in the cost of subcutaneous immunoglobulin preparations associated with development of a properly licenced products. (Personal communication: e-mail from West Midlands Regional Drug Information Service). It may be that this change has alerted commissioners to the high cost associated with IgRT. This systematic review was undertaken to address a regional policy question regarding the clinical and cost-effectiveness of IgRT for immunoglobulin deficiencies at the request of one such commissioner within the West Midlands region.

There are a number of reviews existing on the topic but none included a systematic search of different data sources.[3] [2]Also, health economic assessments were few and potentially misleading as they did not incorporate the recent change in cost of subcutaneous immunoglobulin preparation.

2 Background

2.1 Nature of conditions and epidemiology

The immune system protects the body from potentially harmful substances (antigens) by immune response, which involves two groups of lymphocytes: T-lymphocytes and B-lymphocytes. T-lymphocytes directly attack antigens (cellular immunity, which does not involve antibodies); B lymphocytes produce antibodies (humoral immunity) that attach to the antigen and make phagocytes and body chemicals, such as complement proteins, much more efficient in the destruction of the antigen. Immunoglobulin deficiency (antibody deficiency), also known as agammaglobulinaemia and hypogammaglobulinemia, is a group of conditions where the immune defences do not function properly and is characterized by insufficient antibodies (immunoglobulins) secreted by B-lymphocytes. Immunoglobulin (IG or Ig) is categorized in 5 classes: IgA, IgD, IgE, IgG, and IgM. IgG is the most abundant class in serum and lymph and the main antibody

defence against bacteria. Primary immunodeficiency diseases (PID), which include congenital and acquired antibody deficiency, result from intrinsic defects in the cells of the immune system and are often caused by inherited genetic defects; they usually occur in infancy and are life-long. Secondary immunodeficiency (SID) occurs when the body's ability to produce gammaglobulins (IgG) is affected by another disease (e.g. chronic lymphocytic leukaemia) and can occur at any age. PIDs are grouped according to the part of the immune system that is affected. The WHO recognizes approximately 70 PIDs. There are four main types of PIDs: combined, antibody, complement, and phagocyte. Some types of primary immunodeficiencies are relatively common while others are very rare. Immunoglobulin deficiency is sometimes referred to as hypogammaglobulinaemia. The following are the four main types of primary antibody deficiencies.

- Common Variable Immunodeficiency (CVID);
- X-linked Agammaglobulinemia (XLA)(Bruton's Disease);
- Selective IgA Deficiency (IgAD);
- Severe Combined Immune Deficiency (SCID).

CVID is one of the most frequent of the primary specific immunodeficiency disease with an estimated incidence of 1: 10,000 to 1: 50, 000. Prevalence of IgAD is about 1: 700 in Caucasians but 1: 18,500 in Japanese.[1] The estimated frequency of XLA is approximately 1 in 250,000 in USA and its incidence around the world does not vary significantly.[7] The general estimates of the incidence of SCID are 1 in 75,000-100,000 live births.[8]

Diagnosis of immunoglobulin deficiency is based on the susceptibility to frequent infections and laboratory tests of a decrease or absence of antibodies or specific antibody subclasses.

The main health outcomes associated with hypogammaglobulinaemia are increased susceptibility to infections particularly frequent respiratory and sinus infections, often proceeding to chronic infection and damage (e.g. bronchiectasis).

2.2 Interventions

General

Immunoglobulin replacement therapy is administered by regular infusion of immunoglobulin, which are antibodies (at least 90% of IgG) purified from the blood donated by at least 1,000 volunteer donors. The use of immunoglobulin preparation certainly appears to have a well-established place in reducing infections, which were the main problems associated with hypogammaglobulinaemia prior to the introduction of immunoglobulin replacement. A lifelong replacement therapy by regular immunoglobulin infusion is needed to prevent or control infectious complications of immune deficiency.[1]

Administration

IgRT can be administered by three routes: intravenous infusion (IV), intramuscular injection (IM), and subcutaneous injection (SC). However, IM is nowadays rarely used.

The initial immunoglobulin replacement therapy was subcutaneous injection of immune serum globulin (SCIg), which was used to treat the first patient diagnosed with agammaglobulinemia in 1952. Intramuscular injection of immunoglobulin (IMIG) was soon preferred and became the standard of care for immunodeficient patients in the US and established as the method of choice worldwide. However, IMIG is often poorly tolerated due to pain at injection site; also it may be impossible to maintain levels of plasma Ig sufficient to prevent recurrent infection.[3]

In the late 1970's, slow administration of immunoglobulin by subcutaneous route was introduced for those patients poorly compliant with intramuscular injection to avoid local pain. The type of gammaglobulin used for subcutaneous injection was an intramuscular preparation, which was called Immune Serum Globulin (ISG) and is produced as a 16% solution. Adverse effects of Ig infusion by subcutaneous route are usually mild and local, and the incidence of systemic adverse effects is very rare. SCIG still remains the major route of immunoglobulin

treatment in some countries such as Sweden.[3]

Intravenous infusion of immunoglobulin (IVIg) was explored in the early 1980's, but it was not available until some time later, when serious adverse systemic reactions had been minimized.[3] For the past two decades intravenous preparation has been believed to be a major advance and is the current standard treatment for patients with primary immunodeficiencies, especially with severe antibody deficiencies, in the USA and most of Europe.[2] A disadvantage of long-term IVIg is that it can be complicated by poor venous access and systemic adverse reactions.[4] Also, currently available intravenous preparations differ widely in the manufacturing process, methods of viral inactivation and removal and final composition; the impact of these variables on clinical outcomes is still not clear.[5]

It is an overall consensus that high-dose IgRT is superior to lower doses and it is believed that a minimal trough IgG level of 5g/L should be maintained.[3] Dose or frequency of infusions needed to keep a patient symptom-free depends on the severity of antibody defect and the catabolic rate of infused IgG, because half-life of serum IgG is variable in patients with antibody deficiency.[2]

Home therapy with SCIg has increasingly been used as a replacement alternative to IVIg for adults and children with PID in the past 10 years. The advantage of self-administration of IgG at home is that for patients travel to and from hospital and time off school or work are avoided. Though home-based administration of subcutaneous injection is more feasible than that of intravenous infusion,[1] intravenous self-infusion has become a realistic alternative to hospitalization.[9] In Oxford in the UK, home-based administration of IgRT is used in PID patients but not in CLL patients.

Preparations

Immunoglobulins are manufactured from human plasma that are obtained from large pools of screened donors and may carry a degree of risk of viral transmission.

Manufacturing processes particularly emphasize safety regarding inactivation of non-A, non-B viruses, including hepatitis C.[2]

Immunoglobulin preparations begin with IgG concentrates prepared by either Cohn fractionation (cold-enthanol precipitation/fractionation) or the method of Kistler and Nitschmann. In addition to this, there are various virucidal steps to render the IgG safe for IV infusion including: enzymatic hydrolysis, chemical modification by reduction and alkylation, sulfonation, or treatment with β-Propiolactone, pasteurization, incubation at low pH, and purification by ion-exchange chromatography.[10] Some IVIG products included a heat treatment or detergent solvent step to specifically inactivate viruses.[2] The choices of these subsequent steps depend on the individual manufacturer.

Most IV preparations are produced as 5 or 10% solution.[2] Subcutaneous immunoglobulin preparations are supplied as 15% and 16% solutions. Reported subcutaneous administration of IgG in the studies in the review used IM (Chapel 2000)[3,11] or IV (Remving, 1991)[12] preparations. More recently clinically licenced subcutaneous preparations have been developed. This has however, been associated with an increase in price of SCIg.

Contraindication and adverse event

IgRT is contra-indicated in patients with known class specific antibody to immunoglobulin A (IgA).

There have been no documented HIV transmissions as a result of immunoglobulin replacement therapy.[2,13] Transmission of HBV by IgG also has never been documented. There have been reports of viral transmission of non-A, non-B hepatitis associated with several IVIG preparations, which were related to particular batches.[2] In 2002 the estimated incidence of HCV infection in patients with primary immunodeficiencies from a European surveillance exercise was 8.3%.[14] The prognosis and rate of progression of HCV in PID has been noted to be poorer than in other patients.

Side-effects of immunoglobulins include malaise, chills, fever, etc; analphylaxis is very rare. For intravenous infusion, adverse reactions are common in patients during the first few infusions; newer IVIG preparations are tolerated much better than first-generation preparations. Intramuscular injection of IMIG is painful. There have been no documented cases of HIV or HBV virus transmission associated with IVIG.[2] Adverse events with administration of IgG subcutaneously are mostly mild and local tissue reactions.[6]

Costs

It was reported in 1991 that in Europe the IMIG preparations used for subcutaneous route were less expensive than IVIG preparations.[14] It was also reported in 1994 that the annual retail costs of administering IVIG at a dose of 400mg/kg body weight for a 70kg adult was estimated to be $25,020 to $45,180;[15] in the UK, the average contract price ranged from £10 to £12/g for intravenous IgG preparation[2] and the annual cost of IVIG for self-infusion at home at a dose of 0.4g/kg/month was about £4,500 for a 70kg adult and about £650 for a 10kg infant. It was estimated that home therapy offers a saving for a typical patient of about £800 and $2400-$3600 per year in the added costs of outpatient hospitalisation in the UK and in the USA respectively[2]. The annual costs for hospital-based IMIG and SCIG were similar but the cost of the IVIG was 3-4 times higher, for home-based therapy IGIV was about 4 times higher than SCIG.[6]

However, it seems that over recent years there has been a marked increase in the cost of SCIG preparation. It was reported last year that the average wholesale price of the only regular IMIG currently marketed in the USA is the same as currently available IV preparation.[3] Also, in the UK the current contract price for subcutaneous IgG preparation is about £37/g (personal communication: e-mail from West Midlands Regional Drug Information Service). According to the recent British National Formulary (issue 49), the price for a 10ml-vial subcutaneous IgG preparation is £56 for Subgam® (BPL) (140 -180 mg/ml) or £ 59.20 for Subcuvia® (Baxter BioScience) (160 mg/ml), thus the price per gram is approximately £35 for Subgam and £37 for Subcuvia.

Although it is clear that IgRT preparations are high-cost, there is confusion about the exact level, particularly relative costs of the two main preparations used, IVIg and SCIg. There have clearly been changes in cost over time and it is thus important to consider what effect this has had on past economic evaluations. This will be specifically revisted later in the report.

2.3 Current service provision

A European surveillance showed that in 16 European countries, around 90% of patients with antibody deficiencies receive IVIG in an inpatient setting; around 7.5% of patients are treated with SCIG, mainly at home; only 1.1 % of patients receive IMIG, mainly in an inpatient setting.[16] In the UK, IMIG is not given anymore, only IV or SC routes are used nowadays.

3 Question addressed by review

In July 2004, the Aggressive Research Intelligence Facility (ARIF) at the University of Birmingham was requested by a Primary Care Trust (PCT) in the West Midlands region to advise on evidence on the effectiveness of immunoglobulin replacement therapy for patients with common variable immunodeficiency (CVID). This enquiry identified that although there were some RCTs, particularly comparing alternative methods of administration there were no systematic reviews of these interventions. In addition health economic assessments were few and potentially misleading as they did not incorporate major recent increases in the cost of subcutaneous immunoglobulin preparations. For both these reasons the original requester agreed to sponsor the University of Birmingham to produce a regionally instituted systematic review and health technology assessment.

This report aims to systematically review the available evidence regarding clinical effectiveness and cost-effectiveness of IgRT for primary antibody deficiency (PID) and chronic lymphocytic leukaemia (CLL). The latter was chosen because it represents the most common cause of secondary immunodeficiency which might potentially benefit from IgRT. The questions addressed by the review are:

- Is IgRT effective for immunoglobulin deficiencies?
- Which route of administration of immunoglobulin replacement is more effective, safe, and cost-effective?

4 Methods

4.1 Search Strategy

Scoping search

A scoping search was performed by a trained information specialist to identify appropriate literature concerning the background for the report, to ensure that no previous systematic reviews existed on the topic and to develop the inclusion and exclusion criteria for the review.

Primary completed and ongoing research

A formal search strategy was developed for identifying randomized controlled trials from electronic databases using a validated search filter (**Appendix 1**). The following sources were searched to identify primary studies on the effectiveness and safety of Ig replacement therapy.

- Electronic databases: Cochrane Library (Wiley) 2005 issue 2 for CDSR, DARE, CENTRAL, HTA, and NHSEED), MEDLINE (Ovid) (1966 to 2005 April week 3), EMBASE (Ovid) (1980 to 2005 week 17), and CINAHL (Ovid) (1982 to 2005 April week 4)
- Internet searches
- Citation lists
- Contacting clinical experts
- Registers of trials were searched for unpublished and ongoing trials

The electronic searches were undertaken in April and May 2005. No language restrictions were applied.

Reference lists from reviews identified in the included primary studies were searched for additional relevant primary studies.

4.2 Inclusion/ Exclusion

All titles/abstracts derived through the above search strategy were assessed by ZL; any potentially relevant study from these searches was retrieved for further information. All studies identified were assessed by ZL and checked by EA. Disagreements were resolved by a third reviewer (CH). Only studies that met the following criteria were included:

- **Study design** Experimental studies: randomized controlled trials (RCTs) and quasi-RCTs (i.e. randomization done by alternate order), either parallel or crossover design.

- **Study population** Patients of any age and sex with PID. Selected secondary immunoglobulin deficiencies which are common and require long-term immunoglobulin replacement were also included – this was restricted to chronic lymphocytic leukaemia. The reviews of evidence for PID and CLL were kept separate.

- **Intervention** Any trials analyzing the following treatment options will be considered:

    - IgRT versus placebo, or normal care, or other treatment without Ig replacement;
    - IgRT versus alternative strategy to reduce infection e.g. prophylactic administration of antibiotics;
    - IgRT one route versus another route of administration;
    - IgRT one dose versus another dose;
    - IgRT one variant preparation versus another.

  Difference in setting (administered either at home, or in hospital, or alternate home and hospital) and whether self-administered were also considered.

- **Outcome measures** There was generally no restriction on acceptable outcomes with the exception of chemical outcomes or outcomes of pharmacokinetics, apart from serum IgG level. Studies reporting these outcomes alone were effectively excluded. Although there was no restriction on outcomes, a range of outcomes of particular interest were identified as follows:
-
    - Primary outcomes:
        - ③ Mortality
        - ③ Number (episodes) of infections
        - ③ Severity of infections
        - ③ Duration of infections (or duration of infection-free intervals)
    - Secondary outcomes:
        - ③ Tolerability: adverse reactions (adverse events), viral safety (including infections to HIV and hepatitis), and patient preference
        - ③ Days lost from school or work due to infections
        - ③ Hospitalization (hospital admission)
        - ③ Serum Ig levels
        - ③ Use of antibiotics
        - ③ Quality of life

4.3 Quality

Study quality was assessed by three reviewers (CH, EA, and ZL) independently. Disagreement was resolved by discussion and consensus by the three reviewers. The quality assessment checklist was based on the CRD's 'Quality criteria for assessment of experimental studies'[17] and the Jadad scale.[18] The quality items assessed included the general strengths and weaknesses in relation to selection, performance, assessment and attrition biases. Specific items included method of randomization and allocation concealment; blinding (of investigators, participants,

and outcome assessors); completeness of follow-up; and intention-to-treat analysis.

For crossover trials the following aspects of quality, which are particularly relevant for assessing the quality of a crossover study, were assessed in addition to the above:

- Washout period
- Period effect (treatment period interaction) test
- Number of patients in the sequences (unscheduled crossover rates)

Treatment in the first period of a crossover trial can influence the effect and outcome of the treatment in the second period. Therefore washout periods and order effect tests are important aspects for a crossover trial. A washout period, which was not included in the outcome assessment, was considered to be present if there was a period of time between the 2 treatments.[19] In the same way, in the trials included in the review, immunoglobulin treatment prior to the study entry may influence the effect of subsequent treatment; therefore this aspect was also investigated.

4.4 Data extraction strategy

Data extraction was carried out by ZL and checked by the other two reviewers (EA and CH) using a standardized data extraction form (**Appendix 2**) which was designed based on a sample of included primary studies. Any disagreements were resolved by discussion.

4.5 Data Synthesis

The studies were classified according to clinical condition (PID or CLL) and stratified according to the type of study in terms of IgG delivery routes, dose

range, infusion levels, and types of IgG preparation etc. Each type of these trials was analyzed separately. Results were tabulated and collated in summary tables highlighting any difference and similarities. The results from individual studies were assessed for appropriateness for statistical analysis and data synthesis. Because of the heterogeneity within each type of studies as evidenced by the lack of uniformity in study design, participants, administered doses of IgG and types of IgG preparations, duration of replacement treatment, and methods of reporting outcomes, the results were not appropriate for pooling quantitatively. Identified evidence of the studies was interpreted taking account of the assessment of methodological strengths and weaknesses and the possibility of potential biases.

4.6 Economic evaluation

The starting point for the economic evaluation was a systematic review of studies on cost, health-related quality of life and cost-effectiveness. This suggested extension of the evaluation on three specific aspects of the cost-effectiveness of IgRT for PID. Further specific details of the methods used are provided at the beginning of section 6

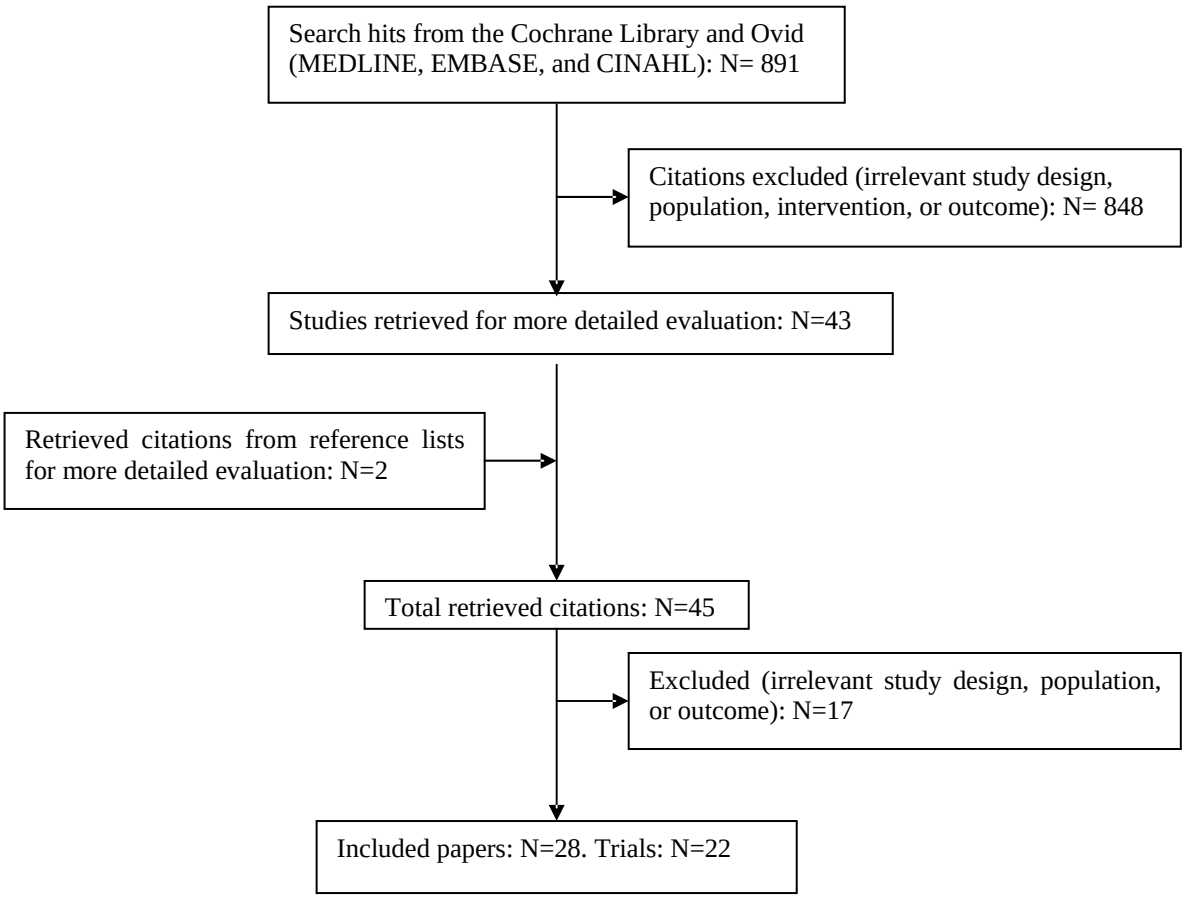
5 Clinical Effectiveness Results

5.1 General quantity of evidence

A total of 22 clinical effectiveness trials (28 reports, including 2 abstract data and 26 full-text papers) met the inclusion and exclusion criteria and therefore were included in the review. The flow diagram below (**Figure 1**) shows how these were obtained. 848 hits from the search strategy were excluded at an early stage, as they were very clearly not applicable. The remaining 43 were retrieved; 2 additional citations were obtained through checking of citation lists and were retrieved.

Of the total 45 retrieved titles/abstracts/citations, 17 were excluded for one or more of the following reasons: study design is not RCT, qRCT or crossover trial (15 studies); outcomes are irrelevant (1 study); irrelevant population (1 study in which patients were low risk B-cell non-Hodgkin-lymphoma (B-NHL)).

Figure 1: Flow diagram of study selection process



In total 22 trials (28 papers, 2 abstracts and 26 full-text publictaions) were included. Of the 22 trials, 2 were reported as an abstract[20,21] and a full-text paper[22,23], 2 were reported as two full-text papers each[24-27], 1 trial was reported in three full-text papers[28-30], and 2 trials were reported in one full-text paper[31]. The remaining 15 trials were represented by one study report each.

Of the 22 included trials, 17 trials studied patients with PID and 5 studied patients with CLL.

The types of the 17 trials with PID patients are as follows: 3 crossover trials studied routes of IgG delivery (2 compared IV with IM[32,33], and 1 compared IV with SC[11]), 3 studied IVIG dose range (1 parallel[34] and 2 crossover trials[23,26,27]), 1 crossover trial studied SC infusion levels[12], and 10 studied the types of IVIG preparation (2 parallel[20,22,35] and 8 crossover trials[10,24,25,31,36-39]).

The types of the 5 trials with CLL patients are as follows: 2 compared IVIG with placebo (1 parallel[28-30] and 1 crossover trial[40]), 2 compared IVIG with no treatment (1 parallel[41] and 1 crossover trial[42]), and 1 parallel trial compared high-dose with low-dose IVIG[43].

The number of titles/abstracts derived is relatively large compared to the number of subsequently included studies. This is due to the fact that there is a large volume of publications relating to immunoglobulin replacement therapy. A wide search filter was used to ensure that all randomized controlled trials were included.

5.2 General quality assessment of evidence

The quality assessment is presented in tables, in which they are classified according to the type of studies, i.e. patient population (patients with PID and patients with CLL) and the nature of comparison, which is the subdivision used to present the results of the included studies. However, for the purposes of a general description of quality the report considers study quality for the parallel RCTs and crossover studies separately in the following paragraphs.

Parallel studies

Only 6 out of the 22 included studies are parallel trials (3 for PID studies[20,22,34,35] and 3 for CLL studies[28-30,41,43]). The quality items assessed for the 6 parallel trials were based on the Jadad scale[18] (score 0-5, including randomization used and method of randomization stated, double blinding used and double blinding of whom stated, and number of withdrawals). The study quality was considered to be inadequate if there was evidence of two or more major threats to internal validity. Jadad score for both the 3 trials in PID patients and 3 trials in CLL patients were 4 for two trials and 2 for one trial. (See **Appendix 3-a**)

All the 6 parallel trials were described as a randomized controlled trial, but only one trial (Roifman C.M., 2003)[35] stated the method of randomization used, which was by a list of unique block random codes supplied by the study sponsor to each pharmacist, revealing the trial preparation allocation to that random number; and the patients were stratified based on bronchiectasis. None of the 6 studies clearly stated the steps taken to conceal allocation.

Four of the 6 trials were described as double-blinded trial and stated that both patients and care providers were blinded, but none of these mentioned whether the outcome assessors were blinded.

Only one trial (Schedel, 1982)[41] had no withdrawal; two trials[22,34] had withdrawal <10%; two trials had withdrawal 33%[28-30] and 27%[43] respectively; in the other trial[35] the number of withdrawals was not clear. Two trials[35,41] did not use the ITT method (of the two one had no withdrawal[41]), the other 4 trials did not mention whether this method was used to analyse the results.[20,22,28-30,34,43]

All the parallel studies had a small sample size except one trial with 162 patients.[35] Only two studies (Roifman C.M., 2003[35] and Eijkout H.W., 2001[23]) calculated sample size. The estimated sample size was achieved in these two studies.

The quality score may be a reflection on inadequate reporting by the authors. However, based on the above quality assessment there are more than two major threats to the validity of the results of most of the 6 parallel studies.

Crossover studies

16 of the 22 included studies are randomised crossover trials (**Appendix 3-b**). The Jadad scale is not an ideal quality assessment tool for a crossover study, e.g. randomization for a crossover trial is not as important as for a parallel trial, as differences in population demographics and disease characteristics are not expected to affect treatment comparisons; also, the Jadad scale does not cover additional aspects that are important for a crossover trial. Therefore, in addition to Jadad scale, other items such as period effects, washout period, and number of patients in sequences were also assessed. All of these 16 crossover studies had evidence of more than 2 major threats to the validity, therefore their study quality was considered as inadequate, except one study by Eijkout H.W., (2001).[23]

Of the 16 studies only 5 trials stated the number of patients in sequences through the whole study duration. In other studies, the number of patients in each treatment arm was ambiguous (this was especially the case after the patients emerged from the first study period into the second). Outcome figures could often hardly be interpreted.

Regarding washout period between two study periods for a crossover study, two of the studies (Garbett N.D., 1989 and Eijkout H.W., 2001[23]) had such a period, 11 studies did not have washout period, and 3 studies did not report whether there was a washout period.

Only two (Remving, 1991[12] and Eijkout, 2001[23]) of the 16 studies carried out a period effect test. Of these two studies, one (Eijkout H.W., 2001[23]) stated that a multivariate model was created in which the number of infections was the dependent variable and dosage, sequence of treatment, and patient were the independent variables, then determined whether the sequence of treatment was

statistically significant; another study (Remvig L., 1991[12]) stated that to avoid carry-over effect from the low-infusion-level period to the high-infusion-level period (and vice versa), the clinical data obtained during these lag periods were not included.
In addition, in some of these studies a number of patients had IgG replacement treatment before the study entry, but there was not a washout period, or a washout/loading period for the comparisons. Therefore, it cannot be ruled out that the treatment before the study had an influence on effect size, or the comparisons were not balanced.

All the 16 studies had a small number of patients. Two of these (Eijkout H.W. (2001)[23] and Roifman C.M., 2003[35]) calculated sample size (on the base of occurrence of infection). The other studies reported no power calculation.

5.3 Effectiveness results for studies involving PID patients

Seventeen trials involving PID patients were identified. 3 of the 17 compared delivery routes (2 compared IV with IM and 1 compared SC with IV), 3 trials studied dose range of IgG, 1 trial compared infusion levels, and 10 studied different types of IgG preparation.

No trials comparing IgRT with placebo or no treatment in PID patients were found.

5.3.1 Trials comparing different routes of delivery in PID patients

(1) IV vs IM

Two fully published RCT crossover trials (Ammann A. J. (1982)[32] and Garbett N. D. (1989)[33]) compared intravenous route with intramuscular route of delivery of IgG. **Table 1** below summarizes the study quality, and **Table 2 and 3** below

summarize characteristics of the trial and patients' baseline characteristics respectively.

The patient pathway and the number of the patients in sequences in both of the trials were not clear; the reporting and methodological quality for both the two trials was very poor. Both of the two studies are very small and no power calculations are reported.

For the two trials, there is some variation in inclusion criteria. Intervention dosage and frequency of administration, and treatment duration were also varied between the two trials. It is not clear whether heterogeneity between the two trials existed, in terms of other baseline characteristics of the patients (age and sex, duration of PID at entry, infection history, previous Ig treatment, and serum IgG level at entry, etc), as data on these aspects was insufficient. It is expected that the actual and potential heterogeneities may have an effect on the treatment and the comparability of the treatment effects between the two studies. Therefore, quantitatively combining the results of these trials was inappropriate.

Primary outcomes

Both the studies assessed outcomes of infections and adverse events (see **Table 4** to **Table 7** below). The study by Garbett N. D. (1989) also assessed some secondary outcomes. The tools used for assessment of the outcomes were not consistent between the two studies.

The study by Garbett N. D. (1989) had an additional study period of 8 patients receiving 3 weekly IV infusion after the two-period crossover study of IVIG (4 weekly) comparing IMIG; the data of this additional period was not included in our analysis.

Both of the two studies showed that outcomes regarding respiratory infections favoured the intravenous route. Ammann A.J. (1982) found that the IVIG group had a significantly smaller percentage of patients with infections in upper respiratory illnesses; Garbett N.D. (1989) found that days with acute respiratory

symptoms in the IVIG group was significantly less than in the IMIG group. (**Tables 4** and **5**)

Secondary outcomes

In the study by Garbett N.D. (1989) IV route was also significantly better than IM route when comparing the events of fever due to infection, days of using antibiotics, days of being unwell, mean serum trough IgG level, and patients' preference. (**Table 6**)

Adverse events

Ammann A.J. (1982) found more adverse episodes with IVIG than in the IMIG group, however the difference was not statistically significant. In the study by Garbett N.D. (1989) data on adverse reactions was insufficient to compare the two routes, but it reported that there were no life-threatening reactions; all patients remained HBV negative. (**Table 7**)

Table 1: Study quality of the trials in PID patients comparing IV with IM

Trial	Randomization method	Concealment	Blinding	Withdrawals (n/N)	Jadad score	ITT	Period effects test	Washout period	N patients in sequences clearly stated	Comments
Ammann, 1982 [32]	Random order by flip of the coin.	NR	No	8/42, 19%	2	No	NR	NR	No	Patients' pathways were not clear. 8 withdrew from IV arm, but from which period not clear.
Garbett, 1989 [33]	Random order but unstated how.	NR	Open label	1/12, 8%	3	Un-clear	NR	4 weeks	No	Patient pathway was unclear. Patients already on IMIG stayed on a 4-week period washout before the first IVIG; newly diagnosed got a 4 weeks IMIG loading of 50 mg/kg/week or started thefirst IVIG. Washout and loading before the second period of study were not clear. Beyond the comparative trial 8 patients had IVIG 3 weekly for 24 weeks; its outcomes were not included in the review.

Table 2: Characteristics of the trials in PID patients comparing IV with IM

Trial	Design	Patient condition	Number randomized	Intervention	Comparator	Study duration*	Outcomes relevant for the review
Ammann, 1982 [32]	Crossover	PID. Of the 42 recruited patients, 7 XLA, 24 CVID, and 3 having immunodeficiency with hyper-IgM.	Total 42. Number in each arm: NR	IV MISG: modified from SIG (immune serum globulin) for IV, prepared by chemical reduction and alkylation of Cohn fraction II, 5% solution (diluted from 10% solution). 300mg/kg every 4 weeks.	IM SIG: Gamastan, a standard immune serum globulin, 16.5% solution. 25mg/kg/ 1 week.	1 year/NR /1 year	Infections, and adverse events

Garbett, 1989 [33]	Crossover	PID. Patients were all with idiopathic panhypogamma-globulinaemia.	Total 12. Number in each arm: NR	IVIG (Intraglobin F): stabilized by β-propiolactone, free of non-specific complement activation, 5% solution. 100mg/month.	IMIG: English standard gammaglobulin. 100mg/kg/month.	24 weeks/4 weeks† /24 weeks	Infection, events of fever, use of antibiotics, serum IgG levels, event of being unwell, and adverse events

* Presented as: period 1 / washout period / period 2.

† See comments from the quality table (Table 1).

Table 3: Patient baseline characteristics of the trials in patients with PID comparing IV with IM

Trial	Age: year(s)	Sex: male%	Population (inclusion / exclusion criteria)	Duration of PID	Infection history	Previous Ig treatment, serum IgG level (unit was converted into g/L)
Ammann, 1982 [32]	Of the 34 who completed the study: 18 ms ~63 ys.	Of the 34 who completed the study: 27/ 34, 79%	**Inclusion**: patients with documentation of a serum IgG concentration <300 mg/dl and failure to form antibody following immunization; must also have no evidence of T-cell system impairment as assayed by four tests: estimation of percentages of T cells, determination of responsiveness to T-cell mitogens and /or allogeneic cells, and evaluation of delayed hypersensitivity skin tests. **Exclusion**: not given.	NR	NR	Individual serum IgG concentration < 3.0
Garbett, 1989 [33]	Median: 31. Range: 19-62	3/12, 25%	**Inclusion**: Patients with idiopathic adult-onset panhypogammaglobulinaemia diagnosed according to the same criteria; asymptomatic during childhood. **Exclusion**: not given.	Unclear. 4 were Newly diagnosed.	Unclear	8/12 were receiving IMIG (25mg/kg/week) and had 4-week washout period before the trial treatment started; 4 newly diagnosed were given 4-week IMIG loading phase (50mg/kg/week) before the trial treatment started if they were assigned to the IMIG arm. Mean trough serum IgG level: 2.0.

Table 4: Primary outcomes of the trials in PID patients comparing IV with IM

Trial	Number of infections	Number of infections per patient	Number of patients infection free	Infection severity (episode)	Duration of infections	Mortality
Ammann, 1982 [32]	Statistically significant (P<0.006) decrease in % of patients with infections in upper respiratory illnesses measured in IVIG group. (See associated **Table 5** below)	NR	NR	NR	NR	NR
Garbett, 1989 [33]*	NR	NR	NR	NR	Days with acute respiratory symptoms: 236 vs 388, p<0.05	NR

* Outcomes are of the intervention IV (4 weekly) vs IM. Outcomes of IV (3 weekly) were not included in the table.

Table 5: Number of patients with acute and chronic infections of the trial by Ammann A. J. (1982) §

Acute (or acute / chronic infections) infections	Percentage of patients with infections	P value (McNemar's test with continuity correction)
Upper respiratory illness	85. 3 vs. 50	0.006
Gastrointestianl tract	55. 9/ 23. 1 vs. 38. 2/ 7.7	0.114/ 0.48
Oitis media	52. 9/ 23. 1 vs. 47.1/15.4	0.772/ 1. 000
Bronchitis	50. 0/ 23.1 vs. 41. 2/ 23.1	0.546/ --
Sinusitis	20. 6/ 23.1 vs. 17. 6/ 15. 4	1.000/ 1. 000
Oral	17. 6/ 0.0 vs. 8. 8/ 0.0	0.371/ --
Conjunctival	29. 4/ 30.8 vs. 26. 5/23. 1	1.000/ 1. 000
Skin	29. 4/ 15. 4 vs. 32. 4/ 0. 0	1.000/ 0.480

§ All observational periods (including the shorter periods due to withdrawal or longer periods due to treatment courses) were adjusted to a 365-day period.

Table 6: Secondary outcomes of the trials comparing IV with IM for PID

Trial	Fever events due to infection	Use of antibiotics	Hospital admission	Absence from school or work	Quality of life or felling of well-being	Serum IgG level (g/L)	Patient preference
Ammann, 1982 [32]	NR	NR	NR	NR	NR	NR	NR
Garbett, 1989 [33] *	Days: 10 vs 30, p<0.05. (Fever: temperature >37.2^{o}C)	Days using antibiotic: 296 vs 511, p<0.05	NR	NR	Days of being unwell: 225 vs 407, p<0.05	Mean trough level: 4.0 vs 3.4, p<0.001	All patients felt better on IVIG than IMIG except 2 felt it inconvenient to attend hospital.

* Outcomes are of the intervention IV (4 weekly) vs IM. Outcomes of IV (3 weekly) were not included in the table.

Table 7: Adverse events of the trials in patients with PID comparing IV with IM

Trial	Number of adverse reaction (s)	Number of patients with adverse reaction (s)	Viral safety
Ammann, 1982 [32]	Total ‡: 49.7 vs 26.5. Anaphylactoid: 0 vs 0	NR	NR
Garbett, 1989 [33] *	40 (of 135 infusions) vs NR Anaphylactoid reaction: 1 vs NR	8 vs NR Anaphylactoid reaction: 1 vs NR	All patients remained negative to acquired hepatitis B

‡ Total: the percentage of administrations with one or more side effects. (Breakdown can be obtained from table 4 in the paper of the primary)

* Outcomes are of the intervention IV (4 weekly) vs IM; outcomes of IV (3 weekly) were not included in the table.

(2) IV versus SC

Characteristics and quality

One small crossover trial with 30 patients by Chapel H.M. (2000)[11] compared IVIG with SCIG in PID patients. The number of patients in sequences was clear during the study, but the withdrawal rate was high (27%) and an ITT method was not used for outcome analysis. There are more than two major threats to the validity, therefore the study is likely to be open to bias (**Table 8-10**)

In this study, for the patients in the UK the IVIG treatment was given at clinic; for the patients in Sweden all treatments were given at one clinic.

Outcomes

In this study there were more infection episodes in IVIG group than in the SCIG group, but in other reported infection events there was no significant difference between the two routes. There was also, no significant difference in terms of days off school or work, serum IgG level, and patient preference between the two routes in this study. (**Table 11-12**)

It can be seen that SCIG tended to have more adverse events than IVIG route, in terms of the number of adverse reactions and number of people with adverse reactions, though these were not statistically tested; however, these reactions were mainly mild and moderate, and local. (**Table 13**)

Table 8: Study quality of the trials in PID patients comparing IV with SC

Trial	Randomization method	Concealment	Blinding	Withdrawals (n/N)	Jadad score	ITT	Period effects test	Washout period	N patients in sequences clearly stated	Comments
Chapel, 2000 [11]	NR	NR	Open label	8/30, 27%	2	NR	NR	No *	Yes	

* Additional information supplied by study author saying that there was a wash-out period.

Table 9: Characteristics of the trials in PID patients comparing IV with SC

Trial	Design	Patient condition	Number randomized	Intervention	Comparator	Study duration*	Outcomes relevant for the review
Chapel, 2000 [11]	Crossover	PID: most of the patients recruited were with CVID.	16 vs 14	IVIG (Endobulin, 5% solution; the same dose as that of the comparator).	SCIG (Gammabulin, 16% solution, IM preparation but used subcutaneously in the study).	1 year/NR /1 year	Days off work or school, serum IgG levels, adverse events, and patient preference to treatment

* Presented as: period 1 / washout period / period 2.

Table 10: Patient baseline characteristics of the trials in PID patients comparing IV with SC

Trial	Age: year(s)	Sex: male%	Population (inclusion / exclusion criteria)	Duration of PID	Infection history	Previous Ig treatment, serum IgG level (unit was converted into g/L)
Chapel, 2000 [11]	Mean 44. Range: 18-67	10/30, 33%	Most of the patients recruited were with CVID. I**nclusion**: Age over 13; PID defined according to WHO classification. **Exclusion**: those had significant thrombocytopenia (plates $<50\times10^9$/L); had high levels of anti-IgA antibodies (>1: 8192); had had severe adverse reactions to a blood product within the last 2 years.	NR	NR	26 were receiving ongoing IVIG, other 4 untreated patients were given loading dose of IVIG until serum IgG trough level consistently >5.0

Table 11: Primary outcomes of the trials in PID patients comparing IV with SC

Trial	Number of infections	Number of infections per patient	N of patients infection free	Infection severity (episode)	Duration of infections	Mortality
Chapel, 2000 [11]	Total (culture positive; major and moderate): 67 vs 45	Sweden: † 4.18 (3.2 - 5.4) vs 4.19 (2.4 - 6.4), P=0.7659 UK: † 4.00 (0 - 6.7) vs 3.00 (0.55 - 6.1), P=0.2188	NR	NR	Sweden ¶: 87 (25-148) vs 73 (29-100), P=0.212 UK ¶: 56 (0-73) vs 25 (7-45), P=0.156	NR

† Mean infection Scores/Patient (combining Major and Moderate Suspected and Confirmed) infections in Each Treatment Period (corrected for 365 days).
¶ Mean (25th to 75th percentile) per 365 days; culture positive, major and moderate infections.

Table 12: Secondary outcomes of the trials in PID patients comparing IV with SC

Trial	Fever events due to infection	Use of antibiotics	Hospital admission	Absence from school or work	Quality of life or felling of well-being	Serum IgG level (g/L) §	Patient preference
Chapel, 2000 [11]	NR	NR	NR	Days (mean (percentiles)): 12 (0-5.5) vs 12 (0-7.8)	NR	Median trough level (quartiles): 7.8 -8.4 (5.8 -9.8) vs 8.0 -9.1 (6.8-2.0)	11 preferred IVIG, 10 preferred SCIG.

§ During the first 6 months of the trial, measured pre-infusion.

Table 13: Adverse events of the trials in PID patients comparing IV with SC

Trial	Number of adverse reaction (s)	Number of patients with adverse reaction (s)	Viral safety
Chapel, 2000 [11]	Mild: 49 vs 151 Moderate: 2 vs 8 Local: 0 vs103 (numbers do not add up) Systemic: 51 vs 53 Anaphylactoid: 0 vs 0	Local reaction: 0 vs 20	NR

5.3.2 Trials involving PID patients studying dose range

Quality

One parallel trial by Ochs H.D. (1984)[34] and two crossover trials (by Eijkhout H.W. (2001)[23] and Roifman C.M. (1988))[27]) compared high-dose with low-dose of IVIG. All of the three are fully published studies. **Table 14** below summarizes the quality of the studies. One crossover study (Eijkhout H.W. (2001)) was judged to be a good quality trial. The quality of the other two trials was affected by evidence of two or more major threats.

Characteristics

Between the two crossover studies, there is some variation in terms of the study population condition and study duration; there is also potential variation in patient baseline characteristics as data on PID duration, infection history, and previous IgG treatment were not clear for both studies. Serum IgG level at entry for the two trials varied. (**Tables 15**-**16**)

For the parallel study data on patient baseline characteristics is not sufficient, thus it cannot be ruled out that differences between the comparison groups may have had an impact on the effect size. (**Tables 15**-**16**)

All three studies assessed outcomes of infection. The studies by Eijkhout H.W. (2001) [23] and by Ochs H.D. (1984) also assessed some secondary outcomes and adverse events. The tools used for assessment of the outcomes were not consistent between the two crossover studies. (**Tables 17** to **19**)

Primary outcomes

In both the studies by Eijkhout H.W. (2001)[23] and by Roifman C.M. (1988)[27], infection episodes in the high-dose groups were lower than in the low-dose groups, and the number of patients free from infection tended to be more in the high-dose group than in the low-dose group; however, the differences between the two doses were not statistically significant. The study by Eijkhout H.W. (2001)[23] also showed that the episodes of total infections per patient were

significantly less, and duration of total infections was significant shorter in the high-dose than in the low-dose groups. The study by Ochs H.D. (1984)[34] did not present detailed data on this outcome but stated that there was no improvement in infections with high-dose in first 12 months. (**Table 17**)

Secondary outcomes

The study by Eijkhout H.W. (2001)[23] suggested that there were better outcomes in terms of fever events due to infection, use of antibiotics, hospital admissions, the number of patients admitted to the hospital, and events of absence from school or work were lower in the high-dose group than in the low-dose group; the days in hospital with high-dose was slightly longer than that in low-dose groups. However, these were not statistically significant. (**Table 18**)

In all these three studies patients in high-dose IVIG had higher serum IgG levels than in low-dose IVIG. In the study by Eijkhout H.W. (2001)[23] serum IgG trough level at both 6 months and the end of the study were significantly higher in high-dose group than in low-dose group. In the study by Roifman C.M. (1988)[27], in those patients receiving high-dose the serum IgG levels increased to 5.0 g/L or more within 2 to 4 months but declined to less than 5.0g/L after switching to low-dose. In those receiving low-dose the serum IgG levels remained well below 5.0g/L but increased to above 5.0g/L within 1 to 3 months after switching to high-dose IgG infusion. The study by Ochs H.D. (1984)[34] also found that serum IgG levels before and after 5th infusion (approximately at 5th month) were higher with the high-dose than that with the low-dose IVIG (not statistically significant); however, it stated that there was no improvement in use of antibiotics and in days missed from school or work with high-dose in first 12 months. Thus, surprisingly it seemed that a higher serum IgG level is more likely to be achieved by higher dose infusion. (**Table 18**)

Adverse events

Both the studies by Eijkhout H.W. (2001)[23] and by Ochs H.D. (1984)[34] showed that high-dose IVIG group had more adverse reaction events than in low-dose group. (**Table 19**)

Table 14: Study quality of the trials in PID patients comparing high-dose with low-dose IVIG

Trial	Design	Randomization method	Concealment	Blinding	Withdrawals (n/N)	Jadad score	ITT	Period effects test	Washout period	N patients in sequences clearly stated	Comments
Eijkhout, 2001 [23] *	Crossover	Computer generated random list	NR	Patients and investigators: yes Outcome assessors: NR	2/43, 5%	5	Yes	Yes, but result NR ¶	3 months	Yes	Good quality of reporting.
Roifman, 1988 [27]	Crossover	NR	NR	No	No withdrawal	2	NA	No	No	Yes	
Ochs, 1984 [34]	Parallel	NR	NR	No	1/35, 3%	2	NR	NA	NA	NA	

* Sample size was calculated.

¶ A multivariate model was created in which the number of infections was the dependent variable and dosage, sequence of treatment, and patient were the independent variables, then determined whether the sequence of treatment was statistically significant.

Table 15: Characteristics of the trials in PID patients comparing high-dose with low-dose IVIG

Trial	Design	Patient condition	Number randomized	Intervention	Comparator	Study duration*	Outcomes relevant for the review
Eijkhout, 2001 [23]	Crossover	PID patients with IgG trough level ≤4 g/L at the time of diagnosis. Excluded those with some conditions.	18 vs 25	Immunoglobuline I.V. Adults: IV 600 mg /kg/4 weeks Children (<20years): IV 800 mg/kg/4 weeks	Immunoglobuline I.V. Adults: IV 300 mg/kg/ 4 weeks Children (<20years): IV 400 mg/kg/4 weeks	9 months/3 months/9 months	Infections, adverse events, having fever, use of antibiotics, hospital admission, absent from school or work, and serum IgG levels.
Roifman, 1988 [27]	Crossover	PID patients with chronic pulmonary disease.	6 vs 6	Sandoglobulin® IV 600 mg/kg, monthly	Sandoglobulin® IV 200 mg/kg, monthly	6 months/NR/6 months	Infections

Ochs, 1984 [34]	Parallel	PID. All have significant B-cell defect. CVID: 14/16 vs 17/18, X-linked: 2/16 vs 1/18.	16 vs 19	Gamimune IV 400 mg/kg/every month	Gamimune IV 100 mg/kg/every month	1.5 years	Infections, serum IgG levels, and adverse events

* Presented as: period 1 / washout period / period 2.

Table 16: Patient baseline characteristics of the trials in PID patients comparing high-dose with low-dose IVIG

Trial	Age: year (s)	Sex: male%	Population (inclusion / exclusion criteria)	Duration of PID	Infection history	Previous Ig treatment, serum IgG level (unit was converted into g/L)
Eijkhout, 2001 [23]	Mean 29.9 Range: 1.6-70.3	27/43, 63%	PID (56% CVID; 44% X-linked agamma-globulinaemia.) **Inclusion**: PID; IgG trough level ≤4 g/L at the time of diagnosis. **Exclusion**: <1 year age; anti-IgA; chronic active disease (e.g. hepatitis, AIDS, malignant conditions); history of anaphylactic reactions to IVIG; participation in a clinical trial 3 months before the start of the study.	NR	NR	4 had SCIG; all others had IVIG. Serum IgG level: 6.3±1.6 vs 6.5±1.7
Roifman, 1988 [27]	Mean: 24 Range: 7-50	8/12, 67%	PID patients with chronic pulmonary disease. **Inclusion**: PID patients with chronic pulmonary disease as established by clinical signs and symptoms of chronic cough and frequent acute exacerbations of pneumonia, radiographic abnormalities of the chest, and pulmonary function tests at least 25% below predicted values. **Exclusion**: Not given	NR	Not clear, all had Chronic lung disease.	Not clear. 5 had regular intramuscular Ig replacement therapy; 5 had over 1-7 years of conventional IgG replacement; the other 3 had not previously been treated using Ig. Serum IgG level for all patients was at least less than 4.0g/L approximately. §
Ochs, 1984 [34]	NR	11/16 (69%) vs 12/19 (63%)	PID patients, all have significant B-cell defect. CVID: 14/16 vs. 17/18, X-linked: 2/16 vs. 1/18. **Inclusion**: patients with PID having a significant B cell defect and normal T cell function. **Exclusion**: Not given	NR	NR	Previous IgG treatment: NG. Serum IgG level (estimated from a figure): 250 vs 150

§ Serum IgG level can be roughly estimated for each patient from figure 1 and figure 2 in the study.

Table 17: Primary outcomes of the trials in PID patients comparing high-dose with low-dose IVIG

Trial	Number of infections	Number of infections per patient	Number of patients infection free	Infection severity (episode)	Duration of infections	Mortality
Eijkhout, 2001 [23]	Total: 100 vs 134 Respiratory infection: 50 vs 61	**Total infections** (mean±SD (95% CI)): 2.5±2.4 (1.8-3.2) vs 3.5±2.6 (2.7-4.3); difference (95%CI): 1.1 (0.4-1.8), P=0.004. **Respiratory infections** (mean±SD (95% CI)): 1.2±1.7 (0.7-1.7) vs 1.5±1.6 (1.0-2.0); p=0.18; difference (95%CI): 0.46 (-0.18-0.78).	Total: 7 v 4	**Total infections:** Mild: 38 vs 54 Moderate: 11 vs 17 Severe: 51 vs 63 ¶	Days (median (range)): Total: 21 (1-125) vs 33 (1-185), p=0.015 Respiratory: 22 (2-125) vs 29 (5 -178), p=0.16	NR
Roifman, 1988 [27]	**Acute minor infections †:** Total: 12 vs 31 Upper respiratory tract infections: 10 vs 23 Otitis: 1 vs 4 Urethritis: 0 vs 1 Skin infections: 1 vs 3 **Acute major infections**: Total: 3 vs 16 Acute exacerbation of lung disease/pneumonia: 3 vs 11 Sinusitis: 0 vs 4 Arthritis: 0 vs 1	NR	**Acute minor infections †:** Upper respiratory tract infections: 3 vs 0 Otitis: 11 vs 10 Urethritis: 12 vs 11 Skin infections: 11 vs 10 **Acute major infections:** Acute exacerbation of lung disease/pneumonia: 9 vs 4 Sinusitis: 12 vs 10 Arthritis: 12 vs 11	NR	NR	NR
Ochs, 1984 [34]	No improvement with high-dose in the first 12 months.	NR	NR	NR	NR	NR

¶ Severe infections: respiratory infections, cellulitis, and sepsis or an infection that resulted in hospital admission.
† Minor infections: did not lead to hospital admission.

Table 18: Secondary outcomes of the trials in PID patients comparing high-dose with low-dose IVIG

Trial	Fever events due to infection	Use of antibiotics	Hospital admission	Absence from school or work	Quality of life or felling of well-being	Serum IgG level (g/L)	Patient preference
Eijkhout, 2001 [23]	Episodes: 32 vs 39 Patients: 18 vs 23 Events per patient (mean): 0.7 vs 1	Patients (therapeutic): 26 vs 32 Patients (prophylactic): 11 vs 11 Antibiotic courses per patient (mean±SD): 1.8±2.5 vs 2.5±2.2	Events: 7 vs 8; Patients: 4 vs 5 Days in hospital (median (range)): 20.5 (9-50) vs 19.0 (5-24)	Events: 0.8 vs 0.8 Days (median (range)): 12.5 (2.0-67) vs 17.5 (1.0-38)	NR	(Trough levels, mean±SD) Months 6: 9.0±2.1 vs 6.4±1.6, p=0.001 Months 9: 9.4±2.7 vs 6.6±1.6, p=0.001	NR
Roifman, 1988 [27]	NR	NR	NR	NR	NR	Can be roughly estimated for each individual from figures in the paper. §	NR
Ochs, 1984 [34]	NR	No improvement in use of antibiotics with high-dose in first 12 months.	NR	No improvement in days missed school or work with high-dose in first 12 months.	NR	Before the 5th infusion: 7 vs 2.5 After the 5th infusion: 16 vs 6.5	NR

§ In those patients receiving high-dose the serum IgG levels increased to 5.0/L or more within 2 to 4 months but declined to less than 5.0g/L after switching to low-dose. In those receiving low-dose the serum IgG levels remained well below 5.0g/L but increased to above 5.0g/L within 1 to 3 months after switching to high-dose IgG infusion.

Table 19: Adverse events of the trials in PID patients comparing high-dose with low dose IVIG

Trial	Number of adverse reaction (s)	Number of patients with adverse reaction (s)	Viral safety
Eijkhout, 2001 [23]	51 (during 35 infusions) vs 36 (during 23 infusions ie mean of 1.6 adverse events during any infusion where there was an adverse event)	13 vs 10	NR
Roifman, 1988 [27]	NR	NR	NR
Ochs, 1984 [34]	During infusion: 13 vs 24 After infusion: 19 vs 12	NR	NR

5.3.3 Trials comparing infusion levels in patients with PID

Quality and characteristics

One very small RCT crossover trial (Remvig L., 1991[12]) with a total of 10 patients compared low- with high-infusion levels of IgG subcutaneously. The IgG preparation used for subcutaneous administration was an intravenous preparation of IgG Nordimmmun®. Though the Jadad score was 4 for this trial, the quality of the study was assessed to be poor, as there was evidence of threats to its validity when assessing other factors, which are important for a crossover trial, such as washout period, number of patients in sequences; also, the high and potentially unequal rate of withdrawals in the two levels of infusion arms may have influence on the validity of the outcomes.

Outcomes

This study did not report outcomes in infection events. Outcomes in terms of events of fever due to infection, days using systemic antibiotics, days in hospital, days missed school or work, and days confined to bed at home all tended to favor high level infusion of IgG. Though the differences are large, they do not appear to be statistically significant.

Adverse events were greater with high-level infusion, but these were all itching or local flushing; no serious side effects were found during the subcutaneous infusions.

Table 20: Study quality of the trials in PID patients comparing low- with high-infusion level

Trial	Randomization method	Concealment	Blinding	Withdrawals (n/N)	Jadad score	ITT	Period effects test	Washout period	N patients in sequences clearly stated	Comments
Remvig, 1991 [12]	NR	Used codes	Yes	2/10, 20%	4	No	Yes †	No	No	The number of patients in the sequences (including withdrawals) through the whole period of the trial was not clear.

† When the IgG dose was changed, the plasma IgG level did not reach the new plateau until a median period of 3 months later. To avoid this carry-over effect from the low-level
period to the high-level period (and vice versa), the clinical data obtained during these lag periods were not included.

Table 21: Characteristics of the trials in PID patients comparing low- with high-infusion level

Trial	Design	Patient condition	Number randomized	Intervention	Comparator	Study duration*	Outcomes relevant for the review
Remvig, 1991 [12]	Crossover	PID patients with indication for IgG-substitution.	Total 10	Nordimmmun® SC, 50 mg/ml, 20 ml per infusion, 2~4 times weekly. Self-administered.	Nordimmmun® SC, 150 mg/ml, 20 ml per infusion, 2~4 times weekly. Self-administered.	12 months/NR /12 months	Days with fever, use of antibiotics, days in hospital, days absent from work, days confined to bed at home, adverse events, and plasma IgG concentration.

* Presented as: period 1 / washout period / period 2.

Table 22: Patient baseline characteristics of the trials in PID patients comparing low- with high-infusion level

Trial	Age: year (s)	Sex: male%	Population (inclusion / exclusion criteria)	Duration of PID	Infection history	Previous Ig treatment, serum IgG level (g/L)
Remvig, 1991[12]	>18. Of the 8 who completed the study: mean 39.5, range 27-57	3/8 (8 were the patients of whom the data were included in the study), 38%	PID patients with indication for IgG-substitution. **Inclusion**: patients with indication for IgG-substitution (recurrent infections and P-IgG< 2.0 g /L or IgG subclass deficiency); age >18 years. **Exclusion**: immunological defects other than hypoimmunoglobulinaemia; malignant disease; prophylactic antibiotic treatment; and pregnancy.	NR	Not clear. All had recurrent infection.	5 patients were on IgG subcutaneous treatment, 1 on intramuscular, 2 without IgG treatment. Plasma IgG level <2.0

Table 23: Primary outcomes of the trials in PID patients comparing low- with high-infusion level

Trial	Number of infections	Number of infections per patient	Number of patients infection free	Infection severity (episode)	Mortality	Duration of infections
Remvig, 1991 [12]	NR	NR	NR	NR	NR	NR

Table 24: Secondary outcomes of the trials in PID patients comparing low- with high-infusion level

Trial	Fever events due to infection	Use of antibiotics	Hospital admission	Absence from school or work	Quality of life or felling of well-being	Serum IgG level (g/L)	Patient preference
Remvig, 1991 [12]	Days with fever: 108 vs 29	Days using systemic antibiotics: 191 vs 85	Days in hospital (total number of days for all patients for each 9-month period): 20 vs 9.	361 vs 43	Days confined to bed at home: 76 vs 10	Can be estimated from figure 1 in the paper.	NR

Table 25: Adverse events of the trials in PID patients comparing low- with high-infusion level

Trial	Number of adverse reaction (s)	Number of patients with adverse reaction (s)	Viral safety
Remvig, 1991 [12]	Itching or local flushing: 0 vs 4	Itching or local flushing: 0 vs 2 (No serious side effects were recorded during approximately 2500 infusions.)	NR

5.3.4 Trials comparing different IgG preparations for PID patients

A total of 10 studies (2 parallel trials and 8 crossover trials) comparing different IgG preparations were identified. All the IgG preparations employed in these reports were used intravenously.

(1) IVIG-C vs IVIG-SD

Quality and characteristics

One small crossover trial (Ballow, 2003 (1))[31] and one medium sized parallel trial (Roifman, 2003[26]) compared IVIG-C with IVIG-SD. The parallel trial is assessed to be adequate as it had a Jadad score of 4, while the quality of crossover trial is assessed to be poor because there is evidence of more than two major threats to the validity. The parallel trial calculated the sample size according to the rate of validated infection and achieved the required size.

The two preparations studied are intravenous products. The IVIG-C, 10% (Gamunex™), is formulated with glycine, without addition of sugar. It is purified by cold-ethanol fractionation, caprylate precipitation and ion-exchange column chromatography; in this product in addition to virus removal by partitioning during purification, enveloped viruses are inactivated by incubation with caprylate. Both enveloped and non-enveloped viruses are inactivated by incubation of the final containers containing IVIG-C, 10% at a low pH (4.25) for 21 days at 23-27^{o}C. The IVIG-SD, 10% (Gamimune® N) is solvent-detergent (SD) – treated; it is also formulated with glycine. [26,31]

Outcomes

The crossover trial was not designed to evaluate efficacy, but pharmacokinetics; it did not have primary outcomes relevant for the review, but stated that there is no significant difference between the two preparations in use of antibiotics, physician or emergency room visits, hospital visits, and days off school or work,

and the mean weekly overall perceived health status scores were nearly identical.

The parallel study shows that in the two preparation groups, the number of patients with validated infections (including sub-category infections) had no significant difference. The number of patients with clinically defined acute sinusitis in IVIG-C treatment is significantly less than in IVIG-SD treatment, though the number of patients with clinically defined infection episodes in all infections was identical in the two groups. The number of patients with both validated and the clinically defined acute sinusitis, and the annual validated infection rate were also statistically proven to favour IVIG-C preparation. However, the outcome analysis was based on 73 patients out of the 87 and 85 patients randomised to the IVIG-C and IVIG-SD group, respectively, who were valid for per-protocol efficacy analysis. Therefore, the evidence may be biased.

Adverse events

In the crossover study there were more adverse events with IVIG-C than IVIG-SD, but there werea similar number of patients with one or more adverse events with these two preparations. There was no evidence of viral transmission related to the IVIG infusion in this study.

In the parallel study, no difference was found in adverse events in patients with the two preparations.

Table 26: Study quality of the trials in PID patients comparing IVIG-C with IVIG-SD

Trial	Design	Randomization method	Concealment	Blinding	Withdrawals (n/N)	Jadad score	ITT	Period effect test	Washout period	N patients in sequences clear
Ballow, 2003 (1) [31]	Cross-over	No	NR	Yes. Whom: NR	No ¶	3	Yes, for safety analysis ¶	NR	Unclear	Yes
Roifman, 2003 [26] *	Parallel	Random code. Stratified.	NR	Patients, Investigators, infusionist and trial nurse: yes. Outcome assessors: NR	Unclear	4	No	NA	NA	No

¶ One patient in control was diagnosed with lymphonma on study, received all infusions, was included in the safety analysis but not pharmacokinetics analysis. ITT for other analysis: NR.

* The sample size was calculated.

Table 27: Characteristics of the trials in PID patients comparing IVIG-C with IVIG-SD

Trial	Design	Population (inclusion / exclusion criteria)	Number randomized	Intervention	Comparator	Study duration*	Relevant outcomes
Ballow, 2003 (1) [31]	Cross-over	**Inclusion**: age ≥18 years; confirmed diagnosis of PID; regular IGIV for ≥ 3 months prior to study entry; at least one documented IgG trough level of ≥ 400mg/dl in the previous 6 months while on the dosing regimen investigated in the study. **Exclusion**: a history of significant allergic reactions to IVIG and /or blood products; selective IgA deficiency (serum level < 5.0 mg/dl) and antibodies to IgA, and isolated IgG subclass deficiency with normal total serum IgG; pregnant or lactating females; with another condition considered to be likely to interfere with evaluation of the trial drug and/or satisfactory conduct of the trial; patients who required more frequent dosing (i.e. every 2 weeks).	9 vs 9	IVIG –C, 10% (Gamunex™, 10%. Formulated with glycine). Average dose: 415 mg/kg every 3 or 4 weeks.	IVIG – SD, 10% (Gaminune®, 10%. Solvent detergent treated). Average dose: 414 mg/kg every 3 or 4 weeks.	9-12 weeks/ unclear/9 -12 weeks	Use of antibiotics, missing school/work, overall perceived health score adverse events
Roifman, 2003 [26]	Parallel	**Inclusion**: with PID, aged 1-75 years receiving IGIV therapy; medical records available for retrospective review for at least 3m prior to study entry; and documented IgG trough level of > 390 mg/dl during the previous 6 months. **Exclusion**: severe infection the day of first infusion; history or suspicion of significant allergic reactions or other blood products; documented history of selective IgA deficiency and known antibodies to IgA, IgG subclass deficiency with a normal total serum IgG level, or any condition which was likely to interfere with the conduct of the trial.	87 vs 85	IVIG-C, 10% (Gamunex™, 10%. Caprylate/ Chromatography). Protocol-specified doses: 100-600 mg/kg, per 3-4 weeks.	IVIG-SD, 10% (Gaminune®N, 10%. Solvent detergent treated). Protocol-specified doses: 100-600 mg/kg, per 3-4 weeks.	9 months	Infections and adverse events

* Presented for crossover study as: first period/ washout period/ second period.

Table 28: Patient baseline characteristics of the trials in PID patients comparing IVIG-C with IVIG-SD

Trial	Age: year (s)	Sex: male%	Patient condition	Duration of PID	Infection history	Previous Ig treatment, serum IgG level (g/L)
Ballow, 2003 (1) [31]	Mean: 37.0 vs 34.1 Range: ≥18	78% vs 63%	No significant differences between the treatment and control groups in age, gender, ethnicity, height, weight, or prior IVIG dosing regimen. Infection histories were similar for the two groups. The most prevalent infection was chronic sinusitis (50%).	NR	NR	Had been receiving regular IVIG infusions for ≥ 3 months prior to study entry. Serum IgG level: Mean ± SD: 8.39± 1.81
Roifman, 2003 [26]	Mean (based on n=73 for each arm and is not ITT): 31.5 vs 29.5. Range: 1-75	(n/N): 51/87 (59%) vs 43/85 (51%)	CVID: 46 (53%) vs 44 (52%). Hypogammaglobulinemia (unspecified): 31 (36%) vs 24 (28%). Congenital hypogammaglobulinaemia: 8 (9%) vs 11 (13%). CID: 1 (1%) vs 5 (6%). Immunodeficiency with increased IgM: 0 vs 1 (1%). Other immunodeficiency: 1 (1%) vs 0.	At least 9 months	Pre-existing bronchiectasis (n/N): 15/87 vs 16/85	IVIG dose: 434mg/kg vs 452 mg/kg. Serum IgG level: NR

Table 29: Primary outcomes of the trials in PID patients comparing IVIG-C with IVIG-SD

Trial	Number of infections	N infections per patient	N patients infection free	Infection severity	Duration of infections	Mortality
Ballow, 2003 (1) [31]	NR	NR	NR	NR	NR	NR
Roifman, 2003 [26] ¶	**Validated infections:** Patients with validated infections: 9 (12%) vs 17 (23%), p=0.060 Patients with acute sinusitis: 4 (5%) vs 11 (14%), P=0.092 Patients with acute exacerbation of chronic sinusitis: 5 (7%) vs 6 (8%), p >0.1 Patients with pneumonia: 0 vs 2 (3%), p >0.1 **Patients with clinically defined infections:** All infections: 56 (77%) vs 56 (77%), p >0.1 Acute sinusitis: 7 (10%) vs 16 (22%), P=0.041 Acute URI, exacerbation of chronic sinusitis, otitis media, bronchitis, acute pharyngitis, conjunctivitis, and pneumonia: no significant difference (P >0.1) **Patients with both validated and clinically defined acute sinusitis:** 11 vs 24, p=0.012 **Annual validated infection rate (mean infections/year):** 0.18 vs 0.44 approximately, p=0.023	NR	NR	NR	NR	NR

¶ Outcomes analysis were of 73 patients in each group, who were valid for per-protocol efficacy analysis.

Table 30: Secondary outcomes of the trials in PID patients comparing IVIG-C with IVIG-SD

Trial	Fever events due to infection	Use of antibiotics	Hospital admission	Absence from school or work	Quality of life or felling of well-being	Serum IgG level (g/L)	Patient preference
Ballow, 2003 (1) [31]	NR	Essentially the same in number of patients using prophylactic antibiotics and the patient-days of prophylactic antibiotics. Patients using of therapeutic antibiotics: 50% vs 61%, but not significant.	Essentially the same in physician or emergency room visits, and hospital visits.	Essentially the same.	Mean weekly overall perceived health status scores were nearly identical.	(Can be estimated from figure 1)	NR
Roifman, 2003 [26]	NR	NR	NR	NR	NR	NR	NA

Table 31: Adverse events of the trials in PID patients comparing IVIG-C with IVIG-SD

Trial	Number of adverse reaction (s)	Number of patients with adverse reaction (s)	Viral safety
Ballow, 2003 (1) [31]	Systemic adverse reactions: ¶ 14 vs 8	Patients with 1 or more adverse event: 16 vs 17	1 patient developed symptoms of viral hepatitis preceding the first treatment with IVIG-C. None of the viral markers investigated, including HCV and HBV, became positive, and symptoms resolved over the course of the study.
Roifman, 2003 [26]	Infusion related: 17.1% vs 18.8% Drug related: 5.7% vs 5.5%	NR	NR

¶ Incidence (number of events during treatment with the designated formulation per number of infusions) of drug-related adverse events occurring in more than one patient during the trial. Drug-related dverse events occurred in more than one patients were: asthenia, headache, back pain, arthralgia, and rhinitis; breakdown can be obtained from the table 4 in the paper of this study.

(2) High-pH vs low-pH IVIG

Quality and characteristics

Two small crossover studies compared low-pH IVIG with high-pH IVIG. The study by Pirofsky (1987)[25] was assessed as of a poor quality of reporting; the quality of the study by Roberton (1987)[39] was relatively better.

There are some variations in the population inclusion criteria and the disease conditions for the two studies. The study duration for the study Pirofsky (1987)[25] was about 12 weeks for each study period, while for the study by Roberton (1987)[39] was 2 months. The washout period was not reported in both of the studies. Data on history of the disease, infection history and baseline serum IgG level in both studies were not given; there might be variation in these between the two studies. Outcome measures for the two trials also varied.

Outcomes

The study by Roberton (1987)[39] was not to investigate the efficacy but incidence of adverse reactions of IVIG. The study by Pirofsky (1987)[25] did not study clinical efficacy either, but showed that infusion of pH 4.25 preparation had a slightly higher total mean elevation of serum IgG level pre- to post-infusion than the pH 6.8 preparation. (**Table 42**)

Adverse events

The study by Pirofsky (1987)[25] showed that the incidence of adverse reaction with low-pH preparation infusion was slightly lower than that with high-pH preparation infusion; however the difference was not statistically tested. The study by Roberton (1987)[39] stated that the low-pH preparation group had significantly less patients with adverse reactions and that the severity of reactions was significantly less with the low-pH IVIG preparation. (**Table 43**)

Table 38: Study quality of the trials in PID patients comparing low-pH with high-pH IVIG

Trial	Design	Randomization method	Concealment	Blinding	Withdrawals (n/N)	Jadad score	ITT	Period effects test	Washout period	N patients in sequences clearly stated	Comments
Pirofsky, 1987 [25]	Cross-over	NR	NR	Yes. Whom: NR	No withdrawal	2	NA	NR	NR	No	
Roberton, 1987 [39]	Cross-over	Yes *	NR	Yes § Whom blinded: NR	No withdrawal	3	NA	NR	NR	Yes	

* Patients were paired (9 pares), one patient in each pair allocated randomly to receive the high-pH IVIG at first infusion and the second patient receiving the low pH preparation.

§ Described as "a blind trial " only. Statistic analyses were done without knowledge of the study code.

Table 39: Characteristics of the trials in PID patients comparing low-pH with high-pH IVIG

Trial	Design	Population (inclusion / exclusion criteria)	Number randomized	Intervention	Comparator	Study duration*	Relevant outcomes
Pirofsky, 1987 [25]	Cross-over	**Inclusion**: patients with PID. **Exclusion**: NG	Total 39	IVIG pH 4.25 (Native. Purified from effluent III by dia- and ultrafiltration, added 10% maltose). 400 mg/kg, every 4 weeks.	IVIG pH 6.8 (Gamimune®, reduced and alkylated. Cutter Biological, Berkley, Calif.). 400 mg/kg, every 4 weeks.	12 wks /NR /12 wks	Adverse events
Roberton, 1987 [39]	Cross-over	**Inclusion**: patients with immunoglobulin or antibody disorders. **Exclusion**: NG	9 vs 9	IVIG low-pH (modified, pH4.0, contained 10% maltose, 10% solution). One infusion.	IVIG standard (pH 6.4, did not contained maltose, 6% solution). One infusion.	Unclear, a 4-wk interval between the 2 infusions.	Adverse reactions

* Presented as: first period/ washout period/ second period.

Table 40: Patient baseline characteristics of the trials in PID patients comparing low-pH with high-pH IVIG

Trial	Age: year (s)	Sex: male%	Patient condition	Duration of PID	Infection history	Previous Ig treatment, serum IgG level (g/L)
Pirofsky, 1987 [25]	Mean: 24	29/39, 74%	Infantile XLA, CVID: 16, Selective IgG deficiency: 2, Wiscott-Aldrich syndrome: 2	NR	NR	All had monthly IVIG, most had for at least 6 months, resulting in a stabilised level of serum IgG. Serum IgG level: not given
Roberton, 1987 [39]	Mean: 10 ys 10 ms. Range: 8ms - 20ys 10 ms	15/18, 83%	SLA: 7; Congenital AG *: 1; Congenital AG with IgM: 4; CVID: 4; Isolated IgM deficiency: 1; Antibody deficiency: 1	NR	NR	All were receiving routine IVIG, 6%, 5.0 - 7.5 mg/kg (300-450mg/kg) per infusion every 4 weeks. Median duration of IVIG therapy for the 18 patients prior to enrolment in the study was 3.5 years (ranged: 1 month to 10 years). Serum IgG level: NR.

* AG: agammaglobulinemia.

Table 41: Primary outcomes of the trials in PID patients comparing low-pH with high-pH IVIG

Trial	Number of infections	Number of infections per patient	Number of patients infection free	Infection severity (episode)	Duration of infections	Mortality
Pirofsky, 1987 [25]	NR	NR	NR	NR	NR	NR
Roberton, 1987 [39]	NR	NR	NR	NR	NR	NR

Table 42: Secondary outcomes of the trials in PID patients comparing low-pH with high-pH IVIG

Trial	Fever events due to infection	Use of antibiotics	Hospital admission	Absence from school or work	Quality of life or feelng of well-being	Serum IgG level (g/L)	Patient preference
Pirofsky, 1987 [25]	NR	NR	NR	NR	NR	Total mean elevation (pre- to post-infusion): 8.52 vs 8.13	NR
Roberton, 1987 [39]	NR	NR	NR	NR	NR	NR	NR

Table 43: Adverse events of the trials in PID patients comparing low-pH with high-pH IVIG

Trial	Number of adverse reaction (s)	Number of patients with adverse reaction (s)	Viral safety
Pirofsky, 1987 [25]	5 (in 115 infusions, 4%) vs 7 (in 117 infusions, 6%)	2 (in 115 infusions, 2%) vs 5 (in 117 infusions, 4%)	NR
Roberton, 1987 [39]	Severity of reactions was significantly less with the low-pH than the high-pH IVIG preparation, p<0.005. Incidence of delayed reactions was the same for both groups.	Patients with adverse reactions: 1 (6%) vs 10 (56%), p<0.01 Patients with minor (no need of intervention) reactions: 1 vs 2 Patients with reaction that required temporary cessation of infusion: 0 vs 6 Patients with reactions that required IV methyl-prednisolone in addition to cessation of infusion: 0 vs 2. Patient tolerance (visual analogue scores) (medians and ranges): patient/parent: 13 (0-90) vs 0 (0-9), nurse: 15 (0-98) vs 2.5 (0-12).	NR

(4) Studies comparing other IVIG preparations

Quality

Five crossover studies and one parallel study compared other IgG preparations. All the studies had small sample size; none of them had a sample size calculation.

In general, study quality of all the 5 crossover studies was poor; the study by Steele (1987)[38] had relatively better quality than the others, but its validity could still be influenced by period effect and potential bias if outcome assessors were not blinded.

For the parallel study, there was evidence of failure to meet at least two major quality criteria. (See **Table 45** below)

Characteristics

The IgG preparations studied as comparisons in the 6 trials were different, though all of them were intravenous preparations and administered intravenously. The characteristics of the IVIG preparations in these studies are summarized below (**Table 44**).

Table 44: Characteristics of variant IVIG preparations

Trial	IVIG preparation in intervention	IVIG preparation in comparator
Ballow, 2003 (2) [31]	**IVIG –C, 5%** (formulated with 10% maltose)	**IVIG –C, 10%**
Ochs, 1980 [37]	**IVIG- maltose** (Cutter Laboratories, Inc., Berkeley, California), packed as 5% solution in 0.1 mol/l glycine with 10% maltose (formulated with 10% maltose), reduced and alkulated.	**IVIG** (Cutter Laboratories, Inc., Berkeley, California), packed as 10% solution in 0.3 mol/l glycine without maltose.
Schiff, 1997 [10]	**Intraglobin-F** (β-propiolactone stabilized) (Biotest Pharma GmbH, Frankfurt Germany. prepared from Cohn fraction II, treated with β-propiolactone. 5% solution.	**Gamimune-N, Sandoglobulin, and Gammagard.** (Normal)
Steele, 1987 [38]	**Unmodified IVIG** (Revlon Health Care Group, Tuckahoe, NY). Native product, containing 5% sucrose, prepared from Cohn fraction II of American plasma by cold ethanol fractionation and lyophilization.	**Modified IVIG** (Gamimune, Cutter Laboratories, Inc., Berkeley, CA) Alkylated, 10% maltose). Reduced, alkylated, and stabilized with 10% maltose.
Zuhrie,	**Alphaglobin**	**Sandoglobulin** (Sandoz);

1995 [36]	(Instituto Grifols SA, Spain), treated with polyethylene glycol fractionation followed by liquid heat treatment (10 h at 60°C), supplied as a sterile 5% solution.	**Gamimune-N** (Bayer)
Wolf, 2003 [22]	**IVIG –N.** Nanofiltered Sandoglobulina, provided as lyophilizates in 6-g vials and was reconstituted to a 6% solution with 100 ml of 0.9% sodium chloride)	**IVIG Sandoglobulina**. Parent product of IVIG-N, provided as lyophilizates in 6-g vials and was reconstituted to a 6% solution with 100 ml of 0.9% sodium chloride.

Apart from that the comparisons of the IVIG preparations in these trials differed, the doses and infusion frequency also varied to some extent. The duration of each study period in these trials varied from 3 months to 12 months. Data on the disease history and infection history of the population was not reported /unclear for all of these studies; other population characteristics, such as inclusion/exclusion criteria, patient condition, previous IgG treatment history, and the reported baseline serum IgG levels, also varied.

In the parallel study, not all the aspects of patient baseline characteristics were comparable between the groups. (**Table 46-47**)

Primary outcomes, secondary outcomes, and adverse events

None of the 6 studies had primary outcomes except one crossover study (Zuhrie, 1995) comparing Alphabulobin with Sandoglobin and Gaminune-N, which assessed scores regarding infection events. (**Table 48-50**)

(a) IVIG-C (5%) vs IVIG-C (10%)

The trial by Ballow (2003) (2)[31] comparing IVIG-C (5%) with IVIG-C (10%) reported that the percentage of patients in IVIG-C (5%) using therapeutic antibiotics was lower than those in IVIG-C (10%), though prophylactic antibiotic use and other clinical parameters were similar and the mean weekly overall perceived health status were almost identical between the comparisons. Also, the IVIG-C (5%) had less drug-related adverse events and patients with adverse events. However, these differences were not statistically tested for significance.

(b) IVIG-maltose vs IVIG (non-maltose)

The trial by Ochs (1980)[37] compared one preparation IVIG-maltose with another preparation IVIG (without maltose) and studied the safety and patient acceptance only. It found that all the adverse reactions were systemic; infusion of the maltose IVIG preparation had much less adverse reactions than that of non-maltose-containing IVIG preparation. The number of infusions with adverse reactions (for all reactions) and the number of patients with adverse reactions (for all adverse reactions) were significantly less in IVIG-maltose group than in IVIG-non-maltose group. The breakdown reactions of these differences were pain, chills, nausea, flushing, chest tightness, and abdominal cramps. The study also found that patient acceptance favoured the IVIG-maltose preparation more than the IVIG-non-maltose preparation.

(c) Intraglobin-F vs Gamimnue-N/Sandoglobin/Gammagard

The trial by Schiff (1997)[10] compared IVIG Intraglobin-F with three other IVIG preparations: Gamimnue-N, Sandoglobin, and Gammagard. The secondary outcomes regarding days with fever due to infection, days using antibiotics, days of hospitalization, days off school or work, score of well-being, serum IgG level, and patient preference showed no significant difference between Intraglobin and the preparations in the comparator. In this study no anaphylactoid reactions occurred; also no adverse events occurred in infusion of Gamimune or Gammagard. The percentage of infusions with adverse reaction and the percentage of patients with adverse reaction when patients receiving Intraglobin-F were higher than those when receiving Sandoglobin preparation; however these differences were not statistically tested for significance.

(d) Unmodified IVIG with modified IVIG

In the study by Steele (1987)[38] comparing unmodified IVIG with modified IVIG, secondary outcomes on fever events, use of antibiotics, hospital admission, and absence from school or work all favored the unmodified preparation; but the average serum IgG levels during the study both immediately following infusion and 4 weeks after infusion were lower with the unmodified IVIG than with the modified IVIG. However, these were not statistically tested. There was no

difference between these two preparations on patient perspective of their general clinical status. This study did not report adverse events.

(e) Alphaglobin vs Sandoglobin / Gaminune-N

The study by Zuhrie (1995)[36] compared Alphaglobin with either Sandoglobin or Gaminune-N. This study measured the infection events as 'weighted mean score of days' and it showed no significant difference between the patients receiving Alphaglobin and receiving Sandoglobin or Gaminune-N. There was also no significant difference between the comparisons in events of fever (due to infection), use of antibiotics, hospital admission, absence from school or work, feeling of well-being, and serum IgG level. Infusion of Alphaglobin tended to have more total and systemic reactions than infusion of Sandoglobin or Gaminune-N.

(f) IVIG-N vs Sandoglobin

One parallel study (Wolf, 2003[22]) compared IVIG-N with Sandoglobin. The outcomes regarding events of using antibiotics, and hospital admission tended to favour Sandoglobin preparation, but the mean score of feeling of well-being favoured the IVIG-N. However, these differences were not statistically proven. The authors also stated that the peak serum IgG levels induced by infusion of the two preparations were comparable. Anaphylactoid reactions occurred once in one patient with Sandoglobin infusion, and the great majority of the adverse events were mild and known to be associated with IVIG products. In general adverse reaction occurred more in patients in IVIG-N infusions than in Sandoglobin infusions. No evidence of viral transmission was found.

Table 45: Study quality of the trials in PID patients comparing other IVIG preparations

Trial	Design	Randomization method	Concealment	Blinding	Withdrawals (n/N)	Jadad score	ITT	Period effects test	Washout period	N patients in sequences clearly stated	Comments
Ballow, 2003 (2) [31]	Cross-over	NR	NR	Open label	1/20, 5%	2	Yes †	NR	NR	No	
Ochs, 1980 [37]	Cross-over	Unclear §	NR	Described as double blind. Patients & investigators: unclear. § Outcome assessors: NR	1/30, 3%	4	No	NR	NR	No	
Schiff, 1997 [10]	Cross-over	NR	NR	Open label	4/27, 15%	1	NR	NR	No	No	
Steele, 1987 [38]	Cross-over	NR	NR	Patients and physicians: yes Outcome assessors: NR	No withdrawal	4	NA	NR	No	Yes	
Zuhrie, 1995 [36]	Cross-over	Alternate order ¶	No Concealment	Open label	No withdrawal	2	NA	NR	No	Yes	
Wolf, 2003 [22]	Parallel	NR	NR	Described as double. Whom: NR	2/36, 6%. (1 vs 1. The one in IVIG group was hospitalized after 4th infusion with fever (40.2^{o}C) and chills.	3	NR	NA	NA	NA	

† Used ITT for safety analysis. For serum IgG level analysis not given.

§ Described as: 'a randomization procedure carried out by the pharmacist from each center who prepared the material for infusion but who was not in direct contact with the patient or the clinician ensured that the study was double blind.'

¶ Quasi-RCT. The first patient in each center was randomly allocated to receive either usual product or the intervention; after that each patient's first product was dependent on the previous allocation.

Table 46: Characteristics of the trials in PID patients comparing other IVIG preparations

Trial	Design	Population (inclusion / exclusion criteria)	Number randomized	Intervention	Comparator	Study duration*	Outcomes relevant for the review
Ballow, 2003 (2) [31]	Cross-over	**Inclusion**: age ≥18 years; confirmed diagnosis of PID; regular IGIV for ≥3 months prior to study entry; at least one documented IgG trough level of ≥400mg/dl in the previous 6 months while on the dosing regimen investigated in the study. **Exclusion**: a history of significant allergic reactions to IVIG and /or blood products; selective IgA deficiency (serum level <5.0 mg/dl) and antibodies to IgA, and isolated IgG subclass deficiency with normal total serum IgG; pregnant or lactating females; with another condition considered to be likely to interfere with evaluation of the trial drug and/ or satisfactory conduct of the trial; patients who required more frequent dosing (i.e. every 2 weeks).	Total 20	**IVIG –C, 5%** Dose was based on the individual patient's pre-study IVIG treatment schedule; average dose 415.00± 95mg/kg/every 3-4 weeks.	**IVIG –C, 10%** Dose was based on the individual patient's pre-study IVIG treatment schedule; average dose 414.00± 95mg/kg/every 3-4 weeks.	9-12 ws/ unclear/ 9-12 ws	Adverse events
Ochs, 1980 [37]	Cross-over	**Inclusion**: patients with PID and had been previously treated with IG or IVIG. **Exclusion**: NR	Total 30	**IVIG- maltose** 100-150 mg/kg, monthly.	**IVIG** 100-150 mg/kg, monthly.	3 ms/NR /3 ms	Adverse event, and patient preference.
Schiff, 1997 [10]	Cross-over	**Inclusion**: PID, aged 1-74 years with severe defects in producing antibodies; had received IVIG for at least 3m prior to the start of the study; a history of mild reaction with acetaminophen or aspirin were allowed to participate and continued to receive the same pre-treatment regimen. **Exclusion**: patients with selective IgA deficiency or a history of an anaphylactic reaction to IVIG.	Total 27	**Intraglobin-F** Between 300 mg and 400 mg/ kg at 3- to 4- weeks intervals, interval between treatment episodes: 3-4 weeks	**Gamimune-N; Sandoglobulin; Gammagard.** Between 300 mg and 400 mg/kg at 3- to 4-weeks intervals, interval between treatment episodes: 3-4 weeks.	6 ms /NR /6 ms	Days with fever, use of antibiotics, hospital admission, absence from work/school, physician visits, days symptomatic, and patient score of well-being.

* Presented as: first period/ washout period/ second period.

Table 46: Characteristics of the trials in PID patients comparing other IVIG preparations (continued)

Trial	Design	Population (inclusion / exclusion criteria)	Number randomized	Intervention	Comparator	Study duration*	Outcomes relevant for the review
Steele, 1987 [38]	Cross-over	**Inclusion**: patients with severe hypogammaglubulinemia. **Exclusion**: NR.	5 vs 5	**Unmodified IVIG** 200mg/kg, with infusions separated by an interval of 4 weeks, interval between treatment episodes: 4 weeks.	**Modified IVIG** 200mg/kg, with infusions separated by an interval of 4 weeks, interval between treatment episodes: 4 weeks.	6 ms /NR/6 ms	Having fever, use of antibiotics, hospital admission, absence from school or work, serum IgG level, and sick days.
Zuhrie, 1995 [36]	Cross-over	**Inclusion**: patients with a diagnosis of PID and aged <75 years, be negative for HBV surface antigen, and had to have at least two normal alanine transferase (ALT) levels within 1 month before the trial. **Exclusion**: NR.	10 vs 11	**Alphaglobin** 16 on 200 mg/kg every 2 ws, 1 on 200 mg/kg once/w, 4 on 300-400 mg/kg monthly. ¶	**Sandoglobulin** (Sandoz); **Gamimune-N** (Bayer). 16 on 200 mg/kg every 2 ws, 1 on 200 mg/kg once/w, 4 on 300-400 mg/kg monthly. ¶	6 ms /NR/6 ms	Days with infection, reaction, fever, antibiotics, adverse event, and visit to doctors; days away off school or planned activity.
Wolf, 2003 [22]	Parallel	**Inclusion**: PID such as CVID, X-LA, or IgG subclass deficiency. **Exclusion**: concomitant other diseases that could interfere with the study; a history of migraine; febrile illness (>38^{o}C); or acute infection within 10 days prior to the first infusion.	19 vs17	**IVIG -N** 0.2 - 0.8 g/kg, at 3- or 4- week intervals, total 8 infusions.	**IVIG Sandoglobulina** 0.2 - 0.8 g/kg, at 3- or 4-week intervals, total 8 infusions.	6 ms	Use of antibiotics; hospital admission; days off work or school; feeling of well –being, and serum IgG level. §

* Presented as: first period/ washout period/ second period.

¶ 16 patients received infusions every 2 weeks, 4 received every 4 weeks, and 1 received weekly.

§ Trough & peak IgG levels (before and after each of the 8 infusions can be obtained from Fig2)

Table 47: Patient baseline characteristics of the trials in PID patients comparing other IVIG preparations

Trial	Age: year (s)	Sex: male (n/N), %	Patient condition	Duration of PID	Infection history	Previous Ig treatment, serum IgG level (g/L)
Ballow, 2003 (2) [31]	Mean: 40.8 vs 33.6 Range: ≥18	55% vs 67%	Patients were generally comparable except that on average the patients were 6.7 years younger in intervention than in control. Rates of abnormal histories were comparable. The most common conditions were chronic sinusitis (45%) and asthma without status asthmaticus (50%).	NR	NR	Had been receiving regular IVIG infusions for ≥3 months prior to study entry. Serum IgG level (mean ± SD): 8.37±1.60
Ochs, 1980 [37]	Mean: 14.4/36.5/ 24.2 (3 centres respectively; mean: 25	20/30, 67%	18 were with CVID, 7 X-linked agammaglobulinaemia, 1 X-linked immunodeficiency with hyper IgM, 2 with Wiskott-Aldrich syndrome, 2 with immunodeficiency involving both humoral and cellular immunity.	NR	NR	Not clear; all had been previously treated with IG or IVIG. Serum IgG level: NR
Schiff, 1997 [10]	Range: 1-74	20/27, 74%	Patients fulfilled the inclusion/exclusion criteria.	NR	NR	All received IVIG for at least 3m prior to the start of the study. Serum IgG level: NR
Steele, 1987 [38]	Range: 19-54	6/10, 60%	PID patients fulfill the inclusion/exclusion criteria. Of the recruited patients: 8 with severe CVID, 2 with severe X-linked congenital agammaglobulinaemia.	Unclear, at least over 1 y.	Unclear, at least over 1 y.	Monthly infusion of native IVIG one year prior to the study; before this time, they had IMIG, most as a weekly dose of 0.22 ml/kg (0.1g /kg /month). Serum IgG level: range 0-2.30.
Zuhrie, 1995 [36]	Range: 28-67	14/21, 67%	PID patients fulfill the inclusion/exclusion criteria. 8 of the recruited patients were with CVID and 2 were with X-linked congenital agammaglobulinemia.	NR	NR	All receiving IVIG (17 Sandiglobulin, 4 Gammiune) Serum IgG level: NR
Wolf, 2003 [22]	Mean: 28 vs 38 Range: (13-56) vs (13-68)	12/19 (63%) vs 10/17 (59%)	The patients were on regular IVIG replacement therapy prior to the study. Patients in the two arms were comparable in regard to gender and body weight. However, patients randomised to Sandoglobulin were older than those on IVIG-N on average. The IVIG-N group included a greater number of patients with recurrent chronic respiratory tract infections (n=10) than the Sandoglobulin group (n=5).	NR	Nuclear	On regular IVIG replacement therapy, details not clear. Serum IgG level: approximately 8.

Table 48: Primary outcomes of the trials in PID patients comparing other IVIG preparations

Trial	Number of infections	Number of infections per patient	Number of patients infection free	Infection severity (episode)	Duration of infections	Mortality
Ballow, 2003 (2) [31]	NR	NR	NR	NR	NR	NR
Ochs, 1980 [37]	NR	NR	NR	NR	NR	NR
Schiff, 1997 [10]	NR	NR	NR	NR	NR	NR
Steele, 1987 [38]	NR	NR	NR	NR	NR	NR
Zuhrie, 1995 [36]	Weighted mean score of days †: with ear infection: 231 (0.01±0.06) vs 230 (.0.01±0.07), p=0.27 with sinus infection 239 (0.31±0.40) vs 242 (0.31 ±0.42), p=0.89 with chest infection 240 (0.34 ±0.40) vs 240 (0.35±0.41), p=0.71	NR	NR	NR	NR	NR
Wolf, 2003 [22]	NR	NR	NR	NR	NR	NR

† Scores were calculated by weighting responses according to severity (0=none, 1=mild, 2=moderate, 3=severe) and dividing by total number of responses (in parentheses).

Table 49: Secondary outcomes of the trials in PID patients comparing other IVIG preparations

Trial	Fever due to infection	Use of antibiotics	Hospital admission	Absence from school or work	Quality of life or feeling of well-being	Serum IgG level (g/L)	Patient preference
Ballow, 2003 (2)[31]	NR	Patients used therapeutic antibiotics: 56% vs 85%. Prophylactic antibiotic use and other clinical parameters were similar between the two groups.	NR	NR	Almost identical in mean weekly overall perceived health status.	(Can be estimated from figure 2 in the primary paper)	NR
Ochs, 1980 [37]	NR	NR	NR	NR	NR	NR	27 preferred Interventio n, 2 had no preference.
Schiff, 1997 [10]	Days ¶ 41 (0-7) vs 47 (0-21)	Therapeutic days ¶: 578 (0-132) vs 451 (0-68) Prophylactic days ¶: 675 (0-184) vs 642 (0-182)	Days ¶: 21 (0-13) vs 0	Days ¶: 405 (0-181) vs 404 (0-181)	Score of well-being § 1.86 (1.0-3.0) vs 1.85 (1.0-3.2)	Mean (SE) (N=24): 654 (50) vs 735 (53), p=0.342.	24 felt both products equivalent.

¶ Sum (range)

§ Mean of 19 patients scored feeling of well-being based on 1 for well to 5 for hospitalized or out of work.

Table 49: Secondary outcomes of the trials in PID patients comparing other IVIG preparations (continued)

Trial	Fever due to infection	Use of antibiotics	Hospital admission	Absence from school or work	Quality of life or feeling of well-being	Serum IgG level (g/L)	Patient preference
Steele, 1987 [38]	Patients: 2 vs 5 Days: 5 vs 17	Patients: 5 vs 7 Days: 79 vs 118	Patients: 0 vs 2 Days: 0 vs 25	Patients: 1 vs 3 Days: 3 vs 29 Sick days/ patients: 116/6 vs 218/7	None patient discerned any difference between the 6m period on the two preparations in their general clinical status.	(Average, during the 12 ms period): Immediately following: 664±204 vs 743±197; 4 weeks after infusions: 338±209 vs 392±198	NR
Zuhrie, 1995 [36]	Mean (SD) proportion of days with fever: 234 (0.00± 0.02) vs 241 (0.01± 0.09), p=0.37	Mean (SD) proportion of days.with antibiotics: 240 (0.53±0.44) vs 240 (0.53±0.45), p=0.62	Mean (SD) proportion of days with visits to doctor or hospital: (0.04±0.15) vs (0.07±0.22), p=0.76	Mean (SD) proportion of days unable attending work or school or planned activity: 238 (0.06±0.18) vs 242 (0.05±0.17), p=0.82	Weighted mean score of days not so well or ill: 239 (0.22±0.34) vs 242 (0.26±0.40), p=0.59 §	Except 1 patient, no significant difference in the serum IgG trough levels between the preparations.	NR
Wolf, 2003 [22]	NR	Patients given antibiotics: 15 vs 8	1 vs 0	Days: 124 vs 102. Patients: 7 vs 6, p=1.000. Mean (range) values for absences (days/m): 0.4 (0-3.3) vs 0.5 (0-3.8), p=0.805.	Mean score of feeling of well-being: 1.9 vs 2.1. ¶ Patients felt 'very poor': 1 vs 1 (following the 4th and 6th infusion respectively)	Peak values were comparable both in patients with 8 infusions of the two preparations at 3-week interval and in patients with 6 infusions of the two preparations at 4-week intervals. ‡	NA

§ Score calculated by weighting responses according to severity (0= well, 1= not well, 2= ill) and dividing by total number of responses.
¶ According to patients' diaries. 1= very well, 5= very poor. Except one in each group felt 'very poor', others considered themselves as 'well'.
‡ Reported for 15 and 13 patients in IVIG-N and control arm respectively; measured immediately before infusion and 15 min after the end of the infusions.

Table 50: Adverse events of the trials in PID patients comparing other IVIG preparations

Trial	Number of adverse reaction (s)	Number of patients with adverse reaction (s)	Viral safety
Ballow, 2003 (2) [31]	Drug related systemic adverse reactions: 1 vs 9 † Drug related headache: 1 vs 5 † Drug related chills: 0 vs 2 † Drug related arthralgia: 0 vs 2 †	15/20 (75%) vs 18/20 (90%) †	NR
Ochs, 1980 [37]	Total number of systemic reactions: 3 vs 82 Number of infusions with side-effects in total 87 infusions: Infusions with all reactions: 3 (3.4%) vs 51 (59%) §, pain: 1 (1%) vs 39 (45%) §, chills: 0 vs 27 (31%) §, nausea: 1 (1%) vs 22 (25%) §. Infusions with flushing: 1 (1%) vs 1 (13%) *, chest tightness: 0 vs 10 (12%) *, abdominal cramps: 0 vs 10 (12%) *. Infusions with anxiety: 0 vs 7 (8%), wheezing: 0 vs 5 (6%), other (dyspnoea, headache, tiredness, red eyes, pallor): 0 vs 8 (8%).	Number of patients with reaction in total 29 patients: - with all reactions: 3 (10%) vs 22 (75.9%) §, pain: 1 (3%) vs 19 (66%) §, chills: 0 vs 14 (48%) §, nausea: 1 (3%) vs 13 (45%) §. - with flushing: 1 (3%) vs 9 (31%) *, chest tightness: 0 vs 6 (21%) *, abdominal cramps: 0 vs 6 (21%) * - with anxiety: 0 vs 5 (17%), wheezing: 0 vs 3 (10%), other (dyspnoea, headache, tiredness, red eyes, pallor): 0 vs 7 (24%).	NR
Schiff, 1997 [10]	Total adverse reactions: 15 vs 16 (Sandoglobulin) Systemic reactions: 10 vs 16 (Sandoglobulin) Infusions with adverse events: 13 in 149 (8.7%) vs 6 in 100 (6%) No anaphylactoid reactions occurred. No adverse events occurred in infusion of Gamimune or Gammagard.	6 (in 26 who received Intraglobun-F, 23%) vs 2 (in 17 who received Sandoglobulin, 11.8%)	NR
Steele, 1987 [38]	NR	NR	NR
Zuhrie, 1995 [36]	Total: 90 vs 67 ¶ Systemic adverse reactions: 90 vs 67 Days with reaction of infusion (weighted mean score of days): 237 (0.05±0.20) vs 238 (0.05±0.17)	NR	Not clear
Wolf, 2003 [22]	Total episodes: 196 vs 107 Episodes of anaphylactoid: 0 vs 1 (The great majority of the adverse events were mild and known to be associated with IVIG products.)	Total: 17 vs 12 Anaphylactoid: 0 vs 1	Patients with HbsAg, HIV p24 antigen and HCV PCR negative pre-study remained negative

† Adverse events of which the incidence occurring in more than one patient during this trial.
¶ Measured in 24 hours of commencing infusion.
§ P<0.02.* P<0.001, McNemar's test.

5.3.5 Summary of results of the studies in PID

(1) IgG vs placebo or no treatment

No evidence on effectiveness of IgG vs no treatment or placebo was found.

(2) IV vs IM

Two crossover RCTs comparing IVIG with IMIG were identified. They were performed in the 1980's. They were small/very small studies (total of 54 subjects of whom 45 were analyzed) with poor methodological quality.

Of the two studies, one found that the IVIG group had a significantly smaller percentage of patients with infections in upper respiratory illnesses; another one found that days with acute respiratory symptoms in IVIG group was significantly less than in the IMIG group. The IV route was significantly better than IM route when comparing the events of fever due to infection, days of using antibiotics, days of being unwell, mean serum trough IgG level, and patients' preference.

One study showed more adverse events in the IVIG group than in the IMIG group, but the difference was not statistically significant. In the other study data on adverse reactions is limited, but it found that all patients remained HBV negative.

(3) IV vs SC

One small (N=30) crossover trial compared IVIG with SCIG in PID patients. The study was conducted in the late 1990's using an IMIG preparation given subcutaneously, there being no specifically licensed SCIG preparation at this time. Unfortunately the validity of the trial is compromised by a high withdrawal rate (27%), without application of a valid ITT analysis exploring the possible effect of the missing data on the results.

This study showed that there were more infection episodes in IVIG group than in the SCIG group, but in other reported infection events there was no significant difference between the two routes. There was also no significant difference in terms of days off school or work, serum IgG level, and patient preference between the two routes in this study.

SC tended to have more adverse events than IV route, but the difference was not statistically proven and the adverse reactions were mainly mild and moderate, and local.

(4) Dose range

One parallel trial and two crossover trials compared high-dose with low-dose of IVIG.

In the parallel trial by Ochs 1984, performed in the early-1980's, the high dose was at the lower end of current suggested dose range and the low dose one quarter of this i.e. well below current recommended doses. In the two crossover trials performed in the mid and late 1980's the high dose was at the upper range of the current normal dose range and the low dose at or just below the lower range of the current recommendations. One of the two crossover studies by Eijkhout 2001 was judged to be a good quality trial while the quality of the other two trials was affected by evidence of two or more major threats. All the three studies were small or very small with the total number of subjects being 90, all but three of whom were included in the analyses.

One study (Eijkhout, 2001) showed that the episodes of total infections per patient were significantly less in the high-dose than in the low-dose groups over the 9 months of each treatment period:

- **Mean total infections**

2.5 vs 3.5

Difference: 1.1 infections per patient less in high dose group (95%CI 0.4 to 1.8)

- **Mean respiratory infections**

1.2 vs 1.5

Difference: 0.46 infections per patient less in high dose group (95%CI -0.18 to 0.78)

The duration of infections was also reduced:

- **Total infections, duration in days (median and range)**

21 (1-125) vs 33 (1-185)

p=0.015

- **Respiratory infections, duration in days (median and range)**

22 (2-125) vs 29 (5 -178)

p=0.16

In the same study serum IgG level in the high-dose group was significantly higher than in low-dose group; outcomes in terms of fever events due to infection, use of antibiotics, hospital admissions, the number of patients admitted to the hospital, and events of absence from school or work also tended to favour the high-dose group; however, these were not statistically proven.

In two of the studies the high-dose IVIG group had more adverse reaction events than in the low-dose group. In the study by Eijkhout 2001 there were 51 adverse events (during 35 infusions) in the high-dose group and 36 (during 23 infusions) in the low-dose group. A rough estimate of the total number of infusions in each period would have been between 350 and 400.

(5) Infusion levels

A very small crossover study (n=10) compared low level of subcutaneous infusion with high level of subcutaneous infusion. The frequency of the

subcutaneous injections was twice to four times weekly. The study quality was assessed to be poor.

No infection events were reported in this study. Outcomes in terms of events of fever due to infection, days using systemic antibiotics, days in hospital, days missed school or work, and days confined to bed at home all tended to favor high-level infusion of IgG, but these were not statistically tested.

High-level infusion tended to have more adverse reactions, but all were itching or local flushing; no serious side effects were found during the subcutaneous infusions.

(6) Type of IgG preparations

(a) IVIG-C vs IVIG-SD

Both recently conducted, one small crossover trial (n=18) and one medium sized parallel trial (n=172) compared IVIG-C with IVIG-SD. The quality of the crossover study is poor. The quality of the parallel trial by Roifman is good, and this combined with its size makes it the bench-mark for any new RCTs in this area. It also calculated the sample size according to the rate of validated infection and achieved the required size.

The crossover trial stated that there is no significant difference between the two preparations in use of antibiotics, physician or emergency room visits, hospital visits, and days off school or work, and the mean weekly overall perceived health status scores were nearly identical.

The parallel study shows that in the two preparation groups, the number of patients with validated infections (including sub-category infections) had no significant difference. The number of patients with clinically defined acute

sinusitis in IVIG-C treatment is significantly less than in IVIG-SD treatment, though the number of patients with clinically defined infection episodes in all infections was identical in the two groups. The number of patients with both validated and the clinically defined acute sinusitis, and the annual validated infection rate were also statistically proven to favour IVIG-C preparation. However, the outcome analysis based on only the number of patients who were valid for per-protocol efficacy analysis flawed the validity of the evidence.

There was no statistically proven difference in the reported adverse reactions in these trials. There was no evidence of viral transmission related to the IVIG infusion.

(b) Low-pH vs high-pH IVIG

Two small crossover studies compared low-pH IVIG with high-pH IVIG (total N=57). In one study the methodology quality was poor, and the other adequate.

Both studies focused on adverse events with no information on infection.

One study showed that the low-pH preparation group had significantly less patients with adverse reactions. This study also stated that severity of reactions was significantly less with the low-pH than the high-pH IVIG preparation. The pattern of reduced adverse events with the low pH preparations was repeated in the second study.

(c) Comparisons of other IVIG types

There were five cross-over studies and one small parallel RCT comparing other types of IVIG preparations. The clinical importance of these comparisons is unclear. However, the small size of all the studies (N ranges from 10 to 36) compromises the ability to conclude that there is no difference in effect or adverse events between any two preparations, particularly as no study reported any power calculations.

5.4 Effectiveness results for studies involving CLL patients

A total of 5 studies involving patients with CLL were included in the review: two studies (1 RCT and 1 randomized crossover study) compared IVIG with no treatment, two studies (1 RCT and 1 randomized crossover study) compared IVIG with placebo, and one RCT compared high-dose with low-dose IVIG. All the 5 studies were fully published.

5.4.1 Trials involving CLL patients comparing IVIG with no treatment or placebo

Quality

Four trials compared IVIG with no treatment or placebo (2 parallel and 2 crossovers). The two crossover trials were very poorly conducted and the reporting was virtually un-interpretable. Of the two parallel trials, the one by Schedel (1982) is judged to be inadequate as the Jadad score was just 2. The other parallel study by CGSICLL (1988) was a good quality study with a Jadad score of 4. It does however, have a very high rate of withdrawal (33%) and it is not clear whether the withdrawals were included in the analysis. (**Table 51** below)

All the 4 trials are small or very small (N ranges from 18 to 42), except one medium size study (CGSICLL 1988) (N=81). None of them had a target sample size derived from a power calculation.

Characteristics

Data on the trial and patient baseline characteristics for the two trials comparing IVIG with no treatment and one trial comparing IVIG with placebo (Boughton, 1995) was limited. There is some variation between the two trials comparing IVIG with no treatment and between the two trials comparing IVIG with placebo, apart from the difference in study design. Also, the placebos used in the two trials comparing IVIG with placebo were different. (**Tables 52-53** below)

Primary outcomes

The study by Molica (1996) found that during the study there were significantly more patients free from infections receiving IVIG than in the no treatment arm. Conversely, the study by Schedel (1982) showed the total number of infection episodes was greater in patients receiving IVIG relative to no treatment. This latter finding was not, however, statistically significant, unsurprising given that there were only 3 events. (**Table 54**)

In the study by Boughton (1995), the percentage of patients who had serious infections (septicaemia and pneumonia) was significantly less in the IVIG group than in the placebo group. 3 deaths were reported in this study, but the treatment group is not stated. The study by the CGSICLL group (1988) measured episodes of bacteria infection and showed that episodes of total bacteria infection were significantly less (p=0.01) in the IVIG group than placebo:

- IVIG: 23 bacterial infections in 41 randomised over 1 year
    - 8 major
    - 10 moderate
    - 5 trivial
- Placebo: 42 bacterial infections in 40 randomised over 1 year
    - 11 major
    - 21 moderate
    - 10 trivial.

The total number of viral infection episodes and the number of fungal or candidal infection episodes were slightly higher in the IVIG group than in placebo group, but these were not statistically significant. (**Table 54**)

Secondary outcomes

None of the 4 studies reported secondary outcomes, except the study by Boughton (1995), which provided information on serum IgG levels.

Adverse events

The study comparing IVIG with no treatment by Molica S. (1996) found that 4 of 22 un-transfused patients who were negative at entry were found to be positive for anti-HCV antibodies while receiving IVIG therapy. The other study comparing IVIG with no treatment (Schedel (1982) reported 1 systemic reaction with IVIG. (**Table 56**)

No serious reaction was reported in the trials comparing IVIG with placebo. The study by Boughton (1995) reported no hepatotoxic virus infection (i.e. instance of any biochemical evidence of transmission of viral hepatitis). (**Table 56**) CGSICLL (1988) reported a small excess of mild adverse reactions in the IVIG treated group.

Table 51: Study quality - trials in CLL patients comparing IVIG with no treatment and IVIG with placebo

Trial		Design	Randomization method	Concealment	Blinding	Withdrawals (n/N)	Jadad score	ITT	Period effects test	Washout period	N patients in sequences clearly stated	Comments
	Molica, 1996 [42]	Cross-over	NR	NR	Patients and investigators: no. Outcome assessors: NR	12/42 (29%) over 6 months; 25/42 (60%) over 12 months	1	Yes	No	NR	No	Very poorly conducted, reporting was un-interpretable. The length of the first period was not clear; number of patients in sequences was not clear through the whole study period, including the withdrawals.
	Schedel, 1982 [41]	Parallel	NR	NR	Patients and investigators: no. Outcome assessors: NR	No withdrawal	2	NA	NA	NA	NA	
	Boughton, 1995 [40]	Cross-over	NR. Randomisation was carried out from the reference centre.	NR	Double blinded. The original or altered treatment codes were not disclosed throughout the 12-month treatment period.	4/42 (9.5%)	3	Un-clear	No	No	No	Very poorly conducted. The patients randomized to IVIG 18g-arm and placebo arm, who when developed 3 or more infections, were switched to IVIG 24g -arm and IVIG 18g- arm respectively; number of patients in sequences were not clear, outcome was un-interpretable.
	CGSICLL, 1988 [28]	Parallel	NR. Stratified according to serum IgG level <4.0 g/L or ≥ 4.0 g/L	NR	Described as double blind. Data analyzing was blinded.	27/81 (33%) §	4	Un-clear	NA	NA	NA	

§ 84 patients were randomised; 3 withdrew after randomisation and before the first infusion (2 refused to participate, 1 developed herpes zoster; but from which arm was not reported); 24 (13 in intervention and 11 in control) didn't finish the full year of 17 infusions (3 died in each group and 5 of the dead were infected at the time of death. 8 stopped for personal reasons and 5 of the 8 had completed 16 of the 17 infusions. 10 other patients withdrew on medical grounds)

Table 52: Characteristics - trials in CLL patients comparing IVIG with no treatment and IVIG with placebo

Trial		Design	Population (inclusion/exclusion criteria)	Number randomized	Intervention	Comparator	Study duration	Outcomes relevant for the review
	Molica, 1996 [42] †	Cross-over	**Inclusion**: patients with IgG levels < 6g /L; and/or a history of at least one serious infectious episode on the 6month period preceding entry into the study. **Exclusion**: NR.	Total 42	IVIG (Ig-Vena N, Italy. 300 mg/kg /4weeks)	No treatment	Not clear	Infections and viral safety.
	Schedel, 1982 [41]	Parallel	**Inclusion**: patients of either sex, between 40 and 80 years of age, who presented with a diagnosis of B cell CLL, characterized by the presence of IgM, IgD, B1 or B41 lymphoid differentiation markers of the malignant B cell clone. **Exclusion**: NR.	11 vs 7	IVIG (Total Ig 12g per 18-26 days, 50 ml/ hour for the first half hour, then 100 ml/hour)	No treatment	6 months	Infections; serum IgG levels; and adverse events.
	Boughton , 1995 [40]	Cross-over	**Inclusion**: patients with CLL and secondary hypogammaglobulinaemia and a history of two or more documented infections in the preceding 12 months, serum IgG <5.5 g/L. **Exclusion**: receiving prophylactic antibiotics in the preceding two weeks or infusions of IVIG or human plasma within the previous 3 months; a severe infection at the time of trial entry; with severe reaction provoked by intravenous blood products.	24 vs 18	IVIG (Sandoglobulin, Sandoz UK. 18g /3 weeks)	Placebo (Human albumin, 0.6g/ 3 weeks, IV)	12 months in total	Infections; serum IgG levels; adverse side-effect; and viral safety.
	CGSICLL, 1988 [28]	Parallel	**Inclusion**: patients with CLL and increased susceptibility to infection (either an IgG level ≤ 50% of the lower limit of normal for the hospital laboratory or a history of one or more serious infections) since the onset of the disease; and patients with low-grade lymphoma who fulfilled these criteria. **Exclusion**: taking prophylactic antibiotics that were reluctant to discontinue; having selective total IgA deficiency, or a history of anaphylaxis after a previous transfusion of blood or blood products.	41 vs 40	IVIG 400 mg/kg, every 3 weeks. Infusions generally completed within 2 hours	Placebo (Equivalent volume of saline, every 3 weeks) Intervals between treatment: 3weeks	1 year	Infections and adverse events.

† During this study 32 patients received chemotherapy; no prophylactic antibiotics.

Table 53: Patient baseline characteristics - trials in CLL patients comparing IVIg with no treatment and IVIG with placebo

Trial		Age: year (s)	Sex: male%	Patients condition	CLL duration, % of Rai stage III & IV	Infection history	Previous Ig treatment, serum IgG level (g/L)
	Molica, 1996 [42]	64 ±11.5	71%	Patients with CLL, and IgG levels < 600mg /dl; and/or a history of at least one serious infectious episode on the 6month period preceding entry into the study; and fulfilled the inclusion/exclusion criteria.	Duration: NR Stage: 62%	Number of patient had history of at least one serious infection in previous 6 months: 17 of 42 (41%).	Not given. Serum IgG <0.5: n =16 ≥0.5<0.6: n=13 >0.65: n=13
	Schedel, 1982 [41]	Not clear (between 40-80)	NR	Patients with CLL and serum Ig concentration < 0.6 g/L; and fulfilled the inclusion/exclusion criteria.	NR	**Intervention** (64%): 5 patients had chronic bronchitis, 1 had skin infection, and another one had urinal tract infection. 4 had no symptoms of infection. **Control** (29%): 1 had urinal tract infection, 1 had fever, and other 5 had no symptoms of infection.	NR. Serum IgG not clear.
	Boughton, 1995 [40]	61±7 vs 63±7 Range: 40-70	62%	Patients with CLL andsecondary hypogammaglobulinaemia and a history of two or more documented infections in the preceding 12 months; and fulfilled the inclusion/exclusion criteria. No significant difference between the comparisons in disease stage, age, height weight, total WBC ($\times 10^9$), PMN	NR	Not clear	NR. Serum IgG: 3.5 ± 0.7 vs 3.6 ± 0.6
	CGSICLL., 1988 [28]	Media (range): 66 (35-82) vs 64.5 (46- 80)	73% vs 63%	Good baseline equivalence on age and sex, duration of disease, disease stage, previous therapy, infection history, and serum IgG level and other laboratory parameters.	Median (range) (months): 50 (6-177) vs 49 (1-168). Rai stage III/IV: 21/41(51%) vs 16/40(40%)	(n/N) None: 5/41 vs 6/40 Occasional: 20/41 vs 21/40 Recurrent or major: 16/41 vs 13/40	No Ig treatment. Serum IgG (mean ± SD (two-tailed) (range)): 4.8± 2.9 (0.6 –16.2) vs 5.1±4.1 (0.6 –25.2)

Table 54: Primary outcomes - trials in CLL patients comparing IVIG with no treatment and IVIG with placebo

Trial		N infections/patients with infections	N infections per patient	N patients infection free	Infection severity (episodes)	Duration of infections	Mortality
IVIG vs No treatment	Molica, 1996 [42]	N infections: 41 vs 62	NR	22 vs 10, p<0.02	Trivial/ minor/major ¶ 6/30/5 vs 11/42/9	NR	NR
	Schedel, 1982 [41]	N patients with infections: 2 vs 1	NR	NR	NR	NR	NR
	Boughton, 1995 [40] §	**N patients with infections**: Failures of all infections: 7 (after 9-11 months) vs 11 (after 5-9 months) Successes of all infections: 17 vs 7 Failures of serious infections: 5 vs 10 Successes of serious infections: 19 vs 8 Serious infections (septicaemia and pneumonia): (21% of 24 patients) vs (56% of 18 patients), p=0.02 Patients experienced ≥ 3 infections: 29% vs 61%, p=0.04	18 of 42 patients had 122 events.	NR	NR	NR	3 patients died during the 12-month study, all from progression of their disease unrelated to treatment with IVIG or the placebo.
	CGSICLL., 1988 [28]	**Bacterial infections**: Total bacterial infections: 23 vs 42, p=0.01. Major: 8 vs 11, p=0.25. Moderate: 10 vs 21, p=0.026 (†). Trivial: 5 vs 10, p=0.10 Bacterial infections in 57 patients (28 vs 29) who completed a full year of treatment: 14 vs 36, p=0.001 **Viral infections**: Total: 40 vs 37, p=0.65. Major: 2 vs 3. Moderate: 6 vs 7. Trivial: 32 vs 27. **Fungal or candidal infections**: 3 vs 2	NR	13 vs 11, p=0.68	(See the number of infections) *	NR	3 vs 3

¶ **Trivial:** infections did not require antibiotic therapy. **Minor**: required no IV antibiotic therapy or hospitalization. **Major**: required IV antibiotic therapy and hospitalization.

§ Outcome of the intervention IVIG 18 g/3 weeks vs placebo. The infectious episodes were defined using an arbitrary scoring system. Treatment failures: patients who experienced ≥ 3 infections.

† Major + Moderate, p=0.026

Trivial: requiring no therapy or at most only symptomatic or topical therapy. **Moderate**: infections requiring oral antibacterial therapy (for example, acute bronchitis, sinusitis, otitis, and urinary tract infection). **Major**: life-threatening infections requiring parenteral antibacterial therapy, hospitalization, or both (for example, septicemia or pneumonia).

Table 55: Secondary outcomes - trials in CLL patients comparing IVIG with no treatment and IVIG with placebo

Trial		Fever events due to infection	Use of antibiotics	Hospital admission	Absence from school or work	Quality of life	Serum IgG level (g/L)	Patient preference
	Molica, 1996 [42]	NR	NR	NR	NR	NR	NR	NR
	Schedel, 1982 [41]	NR	NR	NR	NR	NR	Not clear	N/A
	Boughton, 1995 [40]	NR	NR	NR	NR	NR	The lower limit of the normal range for serum IgG is 8 g/L. § (could be read from figure 1)	NR
	CGSICLL., 1988 [28]	NR	NR	NR	NR	NR	NR	N/A

§ Measured at three weekly intervals in 24 patients who received IVIG on trial entry or in 18 cases that received the placebo.

Table 56: Adverse events – trials in CLL patients comparing IVIG with no treatment and IVIG with placebo

Trial		Number of adverse reaction (s)	Number of patients with adverse reaction (s)	Viral safety
IVIG vs No treatment	Molica, 1996 [42]	NR	NR	4 of 22 un-transfused patients who were negative at entry were found to be positive for anti-HCV antibodies while receiving IVIG therapy.
	Schedel, 1982[41]	Number of patients with systemic reaction: 1 vs 0	NR	NR
IVIG vs Placebo	Boughton, 1995 [40]	No serious adverse side effects form IVIG treatment and only one patient was withdrawn from the trial for this reason.	Total: 21 vs 4. (Pyrexia: 11 vs 2; Lethargy: 3 vs 0; Rigors: 2 vs 1; Sweating: 2 vs 0; Inflamed canula: 1 vs 0; Hypothermia: 1 vs 0. Rigor: 1 vs 0; Headache: 0 vs 1)	No hepatotoxic virus infections, no instance of any biochemical evidence of transmission of viral hepatitis.
	CGSICLL., 1988 [28]	Mild: 16 vs 7. Anaphylactoid events: no	NR	NR

5.4.2 Trial involving CLL patients comparing high-dose with low-dose IVIG

One small parallel trial, with 34 patients (Chapel, 1994) compared IVIG 500mg with 250mg per kg body weight every 4 weeks. The reporting quality of this study is good and has a Jadad score of 4. (See **Table 57** below)

For this one-year study, patient baseline characteristics were equivalent between high-dose and low-dose groups. (Table **58-59**)

Infection events in the two dose groups showed no significant difference. 2 deaths were reported in both the comparison groups. (**Table 60**) No secondary outcomes were reported in this study. (**Table 61**) The low-dose IVIG had more adverse events than the high-dose IVIG, however, no severe adverse events were observed. (**Table 62**)

5.4.3 Summary of effectiveness results in patients with CLL

Quantity and quality of studies

5 fully published studies were identified relating to the effectiveness of IgRT. Of these, 1 parallel and 1 crossover study compared IVIG with no treatment, 1 parallel and 1 crossover study compared IVIG with placebo, and 1 parallel was an IVIG dose range study.

All the studies were small (sample size from 18 to 81). None of the 5 studies reported the randomisation method and concealment. Both of the two crossover trials were very poorly conducted and reported. Of the three parallel studies, 1 comparing IVIG with no treatment was assessed to be of poor quality as it had more than 2 major threats to validity; the other two studies (one compared IVIG with placebo and one studied IVIG dose range) were well conducted and reported.

Clinical effectiveness

With the exception of the smallest study, which had a very small number of events, there was a consistent finding of reduced infection in the IVIG treated groups. The size of this effect was relatively small in the best conducted study by CGSICLL, 1988, and possibly larger in the studies by Molica and Boughton judged to be more open to bias. There was no evidence of a greater effect on infection with higher dose of IVIG in the one study which examined this.

Beyond infection there was relatively little information on secondary outcomes. There was no evidence for an effect on mortality, but it is clear that although deaths were reported testing for an effect on survival was not part of the studies' objectives.

Relative adverse event rates with IVIG were inconsistent. The best conducted study reported a small excess of mild adverse events in the IVIG arm, which is the result most consistent with the findings from the studies in PID. No serious reaction was reported in the trials apart from the one very small study comparing IVIG with no treatment reporting 1 systemic reaction with IVIG. One study comparing IVIG with no treatment found that 4 untransfused patients who were negative at entry became positive for anti-HCV antibodies while receiving IVIG therapy, and one study comparing IVIG with placebo reported that no hepatotoxic virus infection (i.e. instance of any biochemical evidence of transmission of viral hepatitis) was found. Although only one study was encountered which identified HCV conversion, the study reminds that IVIG is a blood product and that stringent measures are required to ensure that infections in donors are not transmitted via blood products.

Table 57: Study quality of the trial in CLL patients comparing high-dose with low dose IVIG

Trial	Randomization method	Concealment	Blinding	Withdrawals (n/N)	Jadad score	ITT	Period effects test	Washout period	N patients in sequences clearly stated	Comments
Chapel, 1994 [43]	NR	NR	Patients and investigators: yes. Outcome assessors: NR	3/16 (19%) vs 6/18 (33%)	4	Un-clear	NA	NA	NA	

Table 58: Characteristics of the trial in CLL patients comparing high-dose with low dose IVIG

Trial	Design	Population (inclusion/exclusion criteria)	Number randomized	Intervention	Comparator	Study duration	Outcomes relevant for the review
Chapel, 1994 [43]	Parallel	**Inclusion**: patients with CLL and an IgG level below the lower limit of normal for the local hospital laboratory or a recent history of one or more serious infections. **Exclusion**: Patients, who were taking prophylactic antibiotics, or had selected total IgA deficiency or a history of anaphylaxis to a blood product.	16 vs 18	High-dose IVIG (500 mg/kg, every 4 weeks)	Low-dose IVIG (250 mg/kg, every 4 weeks)	1 year	Infections and viral safety.

Table 59: Patient baseline characteristics of the trial in CLL patients comparing high-dose with low dose IVIG

Trial	Age: year (s)	Sex: male%	Patients condition	CLL duration, % of Rai stage III & IV	Infection history	Previous Ig treatment, serum IgG level (g/L)
Chapel, 1994 [43]†	63.5±8.4 vs 64.2±8.7	56% vs 72%	Patients with CLL, and IgG levels < 600 mg /dl; and/or a history of at least one serious infectious episode on the 6 month period preceding entry into the study.	Diagnosis to study entry (months) 57.5±45.5 vs 69.8±50.4 Stage: Not given	Patients had 1 or more infection: 11 vs 11 Patients had none infection: 5 vs 7	Previous Ig treatment: NR. IgG level below the lower limit of normal for the local hospital laboratory. 5.1±2.9 vs 5.7±5.2

† No significant difference (P=0.05) on patient baseline characteristics between the comparisons.

Table 60: Primary outcomes of the trial in CLL patients comparing high-dose with low dose IVIG

Trial	Number of infections or patients with infections ‡	Number of infections per patient	Number of patients infection free	Infection severity (episodes)	Duration of infections	Mortality
Chapel, 1994[43]	Total: 23 vs 22, p=0.64 Bacterial (minor/serious): 2/5 vs 2/7 Viral (minor/serious): 5/0 vs 7/2 Fungal (minor/serious): 1/0 vs 1/0 Unknown (minor/serious): 9/1 vs 1/2	Serious bacterial infections per patient-year: 0.30 vs 0.42, p=0.68	Patients free from serious (major and moderate) infections: 11 vs 10, p=0.41.	(See the number of infections)	NR	2 vs 2

‡ Infection episodes in 180 patient-months in high-dose group and 198 patient-months in low-dose group. **Minor**: requiring no antibiotic therapy. **Serious**: combined major (usually requiring intravenous antibiotics and hospitalisation) and moderate (requiring oral antibiotic therapy).

Table 61: Secondary outcomes of the trial in CLL patients comparing high-dose with low dose IVIG

Trial	Fever events due to infection	Use of antibiotics	Hospital admission	Absence from school or work	Quality of life	Serum IgG level (g/L)	Patient preference
Chapel, 1994[43]	NR	NR	NR	NR	NR	NR	NR

Table 62: Adverse events of the trial in CLL patients comparing high-dose with low dose IVIG

Trial	Number of adverse reaction (s)	Number of patients with adverse reaction (s)	Viral safety
Chapel, 1994[43]	2 vs 8 (adverse events were chills, fever, and back pain. No severe adverse event observed)	NR	NR

5.5 Conclusion from clinical effectiveness

5.5.1 PID

Unfortunately, but not unexpectedly, there is no RCT, qRCT or crossover trial evidence on the effectiveness of any IgRT vs no treatment or placebo.

There is limited old evidence that IVIG is more effective than IMIG, particularly with respect to reduced infections. The age of the evidence is important with respect to the nature of the preparations and the doses of IgRT which were being used in the studies. For instance the dose of IVIG is considerably lower than would be used in current practice.

Only one small piece of evidence was identified comparing IVIG vs SCIG, which has been frequently cited to show that the two methods of IgRT are equally effective. Closer examination challenges this somewhat because:

a) the absence of statistical significant differences is more likely to be due to lack of power than absence of any effect
b) there is a consistent trend towards reduced infections, albeit offset to some degree by increases in mild adverse events in the SCIG groups
c) the study is open to bias, particularly through loss to follow-up
d) the study has not been repeated

This suggests that there is more uncertainty than is currently acknowledged.

There is more convincing evidence concerning higher doses of IVIG offering greater reductions in infection but at the cost of slightly increased adverse reactions. The size of effects is best indicated by the following data from Eijkhout, 2001:

- **Mean total infections, number**

2.5 vs 3.5

Difference: 1.1 infections per patient less in high dose group (95%CI 0.4 to 1.8)

- **Total infections, duration in days (median and range)**

21 (1-125) vs 33 (1-185)

p=0.015

- **Adverse events**

51 (during 35 infusions) vs 36 (during 23 infusions)

[Total number of infusions in each period would have been between 350 & 400]

In general the quality of all the evidence is undermined considerably by the small size of studies and threats to validity. Given the reliance on crossover studies in this area of clinical research, understanding about the appropriate reporting and analysis of these study designs appears limited. The studies were often done many years ago when methodological standards were not as clearly defined.

Finally the rigorous studies sought in this systematic review provided no information on the potentially extremely important effects of IgRT relating to survival and rates of organ damage secondary to chronic infection, especially bronchiectasis.

5.5.2 CLL

In contrast to PID there is evidence comparing IVIG with no treatment or placebo. Although this evidence is undermined by threats to validity, it is clear that IgRT can reduce the incidence of infections in CLL. The result from the best conducted RCT suggests that this effect although statistically significant is modest. Further there is no evidence from the one RCT which addressed this question that higher doses of IgRT bring about greater reduction in infections.

There is no information on outcomes other than infection and inconsistent evidence on adverse events, which is probably most compatible with there being a small excess of mild adverse events associated with IVIG. One study in Italy in 1996 identified four cases of HCV infection likely to be due to the IVIG given in the study in question.

As for PID, comments about poor study conduct apply equally to the studies of CLL, particularly crossover studies which are if anything worse.

6 Health economic evaluation

6.1 General approach

The pre-stated approach in the protocol was to start with a systematic review of the existing research on cost, quality of life and cost-effectiveness of IgRT in PID and CLL. If sufficient data was available, a cost-effectiveness model was to be developed. Where effectiveness was shown to be similar for different types of IgRT a cost minimization analysis was to be conducted. If effectiveness varied, cost-effectiveness was to be expressed as cost per infection avoided. Expressing results as cost per QALY was also to be explored as an option.

In the event the specific components of the health economic evaluation were substantially shaped by the findings of the systematic reviews of both effectiveness and cost-effectiveness. This will be explained in detail at the end of the next section describing the method and results of the systematic review.

6.2 Systematic review of health economic literature

6.2.1 Method

The aim was to identify and summarise all relevant research literature on:

- Cost of IgRT in PID and CLL
- Health economic evaluations of IgRT in PID and CLL
- Health-related quality of life in IgRT in PID or CLL

Searches were conducted of MEDLINE (Ovid) (1966 to July 2005), NHS EED via the Cochrane Library (Wiley) 2005, Issue 2 and OHE HEED July 2005 Issue. Details of the search strategies are provided in Appendix 3. In brief the search

strategies targeted studies which had the conditions of interest (primary or secondary immune deficiencies and synonyms thereof) and the interventions of interest (immunoglobulins and synonyms thereof) and the study type (cost studies or economic evaluations or quality of life studies). The resulting hits were screened by one reviewer (CH), any article which appeared potentially relevant being ordered in full. Final decisions on inclusion were made on the basis of the full text by the same reviewer. Studies were included if the article did indeed provide useful information on cost, cost-related to outcome or on health-related quality of life. No methodological restrictions were applied. Details and results of the included studies were abstracted. The results are primarily presented as summaries of each included study. Key aspects of study quality were considered when drawing conclusions. The features highlighted by Drummond et al were those used in the assessment of studies of cost and cost-effectiveness.

6.2.2 General results

There were 152 hits from the searches. 13 studies appeared sufficiently likely to be relevant based on the title and abstract for the full text to be ordered. One of these could not be obtained because of incomplete referencing information (absent page numbers) on the database (OHE HEED).

Of the 12 studies which were obtained:

- 3 studies were included as health economic evaluations of IgRT in PID.[44-46] The first compared IVIg with IMIg.[44] The second two compared IVIg with SCIg. [45,46]
- No studies were formally included as cost studies in PID, although all the health economic evaluations provide information on cost.

- Four studies were included addressing health-related quality of life in PID.[47-50]
- One study was included as a health economic evaluation of IgRT in CLL.[51]
- There were no included studies addressing either cost or health-related quality of life in CLL

Two of four excluded papers were “follow-up” studies of PID patients which on closer examination provided no directly relevant health economic information.[52,53] One excluded paper was a pre-post study of CLL patients suffering recurrent infections started on low dose IVIg, but again with no estimates of cost, cost-effectiveness or health-related QoL.[54] One excluded study was a journal letter mentioning high cost of IgRT without providing details of how the costing was arrived at.[55]

6.2.3 Economic evaluations of IgRT in PID – IMIg vs IVIg

The study by Galli et al 1990 undertook a pre-post study assessing the impact of changing IMIg to IVIg in 23 children with PID. 10 of these were CVID, 8 X-linked hypogammaglobulinaemia and 5 ataxia telangectasia. The following were measured in the 2 years prior to and three years following the change, at 3 weekly assessments:

- Number of days with antibiotics
- Number of absences from school
- Number of days in bed/hospital
- Number of days with infection fever

It is unclear whether all those who started the study were included in the final data and whether the data collected in the assessments were corroborated in any way. For both these reasons the reported results are open to bias. With these provisos, the study reports major reductions in all the clinical events recorded. Most pronounced was the change in hospital bed days – to 10% of the

pre IVIg level; least pronounced was the reduction in school absences – to 50% of the pre-IVIg level. Unfortunately the absolute levels are not quantified. The changes in events were accompanied by substantial increases in serum Ig levels (100mg/dl on average to >500mg/dl). None of the children suffered serious adverse events associated with IVIg, suggesting that benefits were not off-set by increased adverse events. The pattern and size of the clinical effects are similar to those observed in the cross-over trials of IMIg vs IVIg included in the systematic review described earlier in this report.

The study then attached costs to IgRT, hospitalisation and antibiotic therapy for the case of a 20kg child treated with IMIg and IVIg. The relative costs/month in Italian Lire (cost year unstated, but presumed to be before the publication date of 1990) were given as:

- IMIg
    - Antibiotic therapy 233.000
    - Hospitalisation 560.000
    - Ig therapy 160.000
    - TOTAL 953.000
- IVIg
    - Antibiotic therapy 58.000
    - Hospitalisation 300.000
    - Ig therapy 468.000
    - TOTAL 826.000

This suggests that the marked increases in costs associated with IVIg are more than off-set by reductions in costs associated with antibiotic treatment and hospitalisation.

The strength of this conclusion is however considerably undermined by a complete absence of information on the data which were used derive the cost figures.

6.2.4 Economic evaluations of IgRT in PID – IVIg vs SCIg

Both studies in this category examined the cost-effectiveness of IVIg relative to SCIg as the route by which IgRT is given. Both studies used a cost-minimisation approach, in which the effectiveness of each alternative is considered to be equal. The main feature differentiating the two options is thus cost, and the option costing least is deemed preferable.

Gardulf's et al 1995 study's main focus was actually on recording the side-effects and patient perceptions of 165 patients with PID (mostly CVID) receiving sub-cutaneous IgRT. The main finding related to the apparent safety of SCIg, which seems well founded given the very low level of adverse reactions relative to the number of patient-years of observation. Unfortunately, the basis of the conclusions concerning cost seems less secure. The first issue is how costs on IM and IV administration are derived given that the data collected in the paper relate to patients receiving SCIg. The part of the methods section dealing with costs provides some information and suggests that the costing exercise may have been completely separate. The costs quoted are said to be those of IgRT to the Swedish health care system and included:

- Immunoglobulin preparations (dose 400mg/kg per month as suggested by WHO)
- Materials
- Personnel
- Rooms and administrative overheads

There is a note suggesting that immunoglobulin products might be less costly in Sweden. The cost year is 1993 and the original costs in Swedish kronor are converted to US$ using an exchange rate of 7.8 Swedish kronor to 1 US$.

On these bases the annual costs of five alternative route/setting combinations were calculated as:

- Hospital/IM 3,204 $US per annum
- Hospital/IV 14,124 $US per annum
- Hospital/SC 4,656 $US per annum
- Home/IV[†] 13,224 $US per annum
- Home/SC 3,096 $US per annum

Although it is an implicit assumption in the cost comparison presented in the paper by Gardulf et al, it is not clear that the evidence for equivalent effectiveness has been carefully scrutinized. Such a conclusion could not be derived from the data presented in the paper, nor is there a systematic review of the available effectiveness evidence comparing IVIg with SCIg.

The more recent study by Hogy et al 2004 is explicitly a cost-minimisation analysis comparing costs of IVIg and SCIg. Although not completely clear, it appears to be an assumption that IVIg is given in an out-patient clinic and SCIg is given at home. The basis for the assumption of equal effectiveness is the cross-over study by Chapel et al 2000. As indicated earlier in this report this is the best study to use to examine this assumption. Unfortunately although superficially the study by Chapel et al provides support for equivalent effectiveness, this is not unequivocal for the following reasons:

- The study is probably underpowered and has insufficient numbers to exclude small but potentially clinically important differences in effects
- The study actually shows trends towards reductions in infections with SCIg
- There were problems with the conduct of the study which may undermine the conclusions. The most serious challenge to validity was a loss to follow-up of 27%.

[†] Misprinted in results table as Home/IM

Hogy et al compared costs from the perspective of the German statutory health insurance system. The quantity of resources used to deliver IVIg or SCIg were derived from a survey of 18 PID-treating centres in Germany. The costs for each unit were taken from standard tariffs for drugs and out-patient health services in Germany for 2003. The resources and costs in Euros are measured over a period of one year. The costs considered were:

- Immunoglobulin preparations (dose again 400mg/kg per month)
- Medication for premedication
- Infusion materials or pumps
- Treatment by physician and diagnostic procedures
- Sick leave for childrens caregivers

Any resource use which was not different between IVIG and SCIg was not included in the calculations. This included resources associated with treatment of complications, which in keeping with the cost-minimisation approach were considered to be equal. Costs were summed using a simple formula and the sensitivity of the difference in cost between IVIg and SCIg to alternative assumptions tested.

The resulting base case costs were:

- Adults IVIg 31,027 € (30,456 € Ig costs)
- Adults SCIg 14,893 € (13,874 € Ig costs)
- Children IVIg 17,329 € (16,243 € Ig costs)
- Children SCIg 8,659 € (7,400 € Ig costs)

On this basis there is a marked difference in cost between IVIg and SCIg for both adults and children. This difference is mainly driven by unit costs of IVIg and SCIg which were € 86.40/g and € 38.54/g.

6.2.5 Cost studies of IgRT in PID

As indicated there were no cost studies, although the economic evaluations discussed in the previous sections provide information on costs.

6.2.6 Health-related quality of life in PID

Four studies measured health related quality of life in PID. The first two assessed quality of life in patients receiving IVIg; Zebracki et al measured this in children;[47] Tcheurekdjian et al in adults. [48] Two studies by Gardulf et al focused on the change in health-related quality of life when transferring to home-based SCIg; in the earlier study the starting point was either IMIg, IVIg or no treatment;[49] in the later one it was hospital based IVIg.[50]

In the study by Zebracki 36 children with IVIg treated PID, 36 children with juvenile idiopathic arthritis and 36 healthy children were assessed using the Child-Health Questionnaire-Parent Report version (CHQ-PF50). The children ranged in age from 4 to 18 years. The measurements showed marked reductions in quality of life for both PID and juvenile idiopathic arthritis relative to healthy children. The reductions were more marked for physical than psychosocial dimensions of the assessment tool. Tcheurekdijan et al carried out a similar exercise in 58 adults with IVIg treated CVID. 57% were receiving IVIg as hospital outpatients and 43% at home. Health-related quality of life was measured using SF-36. The scores obtained were of a similar level or worse (especially the general health domain) than age and sex matched scores for two other chronic conditions, diabetes mellitus and congestive heart failure.

The study by Gardulf et al in 1993 examined the effect of starting SCIg, initially in hospital and later transferring to home, on health-related quality of life. This was measured using the Sickness Impact Profile and the General Health Rating

Index. Impact on infections and immunoglobulin levels was also measured. There were two distinct groups; 15 persons already receiving treatment with IVIg or IMIg; and 10 persons untreated with IgRT. The age range was 18 to 66 years with a mean of 43, most of whom had CVID. The scores for the Sickness Impact Profile were given as being worse than an equivalent normal population before SCIg treatment, more markedly so for those previously untreated; the differences between all patients treated and the normal population had diminished after 18 months of SCIg treatment, as did the size of the difference in quality of life between previously untreated and previously treated patients. The actual pre-post changes in the SIP scores were not given. For the General Health Rating Index the mean total score increased from 62 to 72 (maximum score 110), mirroring the pattern of improved health seen with the Sickness Impact Profile. As well as improvements in general health status, Gardulf et al also identified a reduction in the number of infections as follows:

- Hospital admissions over 18 months
- Before SCIg 5 patients for mean of 17 days Overall mean 2.27 d/yr
- After SCIg 1 patient for 5 days Overall mean 0.13 d/yr
- Visits to doctor over 12 months
- Before SCIg Mean 7 visits per patient per year Range 1 to 27
- After SCIg Mean 3 visits per patients per year Range 1 to 6

Improvements in recreational and social activities were also measured as were marked increases in serum immunoglobulin levels:

- Previously treated (IMIg and IVIg) (n=15)
- Before SCIg Mean 440mg/dl SD 300 Range 70-1250 mg/dl
- After 18 m SCIg Mean 980mg/dl SD 150 Range 750-1250 mg/dl
- Previously untreated (n=10)
- Before SCIg Mean 190mg/dl SD 150 Range 20-420 mg/dl
- After 18 m SCIg Mean 910mg/dl SD 130 Range 700-1090 mg/dl

The article by Gardulf et al 2004 describes a similar study to the one in 1993 looking at the changes in health-related quality of life and treatment satisfaction associated with a change to home-based SCIg. Key differences were: that children (defined as under 14 years)(n=17) as well as adults (n=41) were examined; and the initial treatment was hospital-based IVIg (with the exception of 10 adults who were included to act as controls). It is also worth noting that there may have been differences in the efficacy and side-effects of the IVIg preparations in operation in the 1993 study and those in the study in 2004. The study was international and multi-centred. Health-related quality of life was measured using Child Health Questionnaire – Parental Form 50 (CHQ-PF50) or SF-36 for children and adults respectively, each of which was measured at baseline, 6 months and 10 months. There was some loss to follow-up (2/17, 12% for children; 9/41, 22% adults). The baseline serum IgG levels were close to current target treatment levels: children mean 790 mg/dl (range 550 to 1190); adults 830 mg/dl (range 590 to 1580).

The results for children were that of the 14 concepts captured by CHQ-PF50 all showed improvement or no change following the change to home-based SCIG after 10 months. Among the 14 concepts there were 5 showing statistically significant improvements in general health, parent impact – emotional, parent impact – time, family activities and global health. Treatment satisfaction, measured on Life Quality Index scale also increased from 74 to 95 (max score = 105).

For adults there were statistically significant improvements for vitality, mental health and social functioning. The results for other domains of the SF-36 i.e. physical functioning, role-physical limitations, bodily pain, general health and role-emotional limitations, are not given. The SF-36 scores for the 10 “control” adults were stated to be high at baseline and showed no statistically significant changes over time. Like children, there was marked improvement in treatment satisfaction for the 22 adults changing from IVIg to SCIg, Life Quality Index scale

changing from 82 to 94. In contrast the 10 control adults score was 96 at baseline and 95 at 10months.

6.2.7 Economic evaluations of IgRT in CLL

Only one study was identified providing any information on cost, quality of life or cost-effectiveness of IgRT for chronic lymphocytic leukaemia. This was an economic evaluation by Weeks et al.[51]

Weeks et al developed a decision-analytic model to assess the cost-utility of using IVIg, at a standard dose of 400mg/kg every 3 weeks, compared to placebo. A societal perspective was claimed, but the actual approach adopted was from that of a health service provider, as no costs to patients, family or society at large were included. Effectiveness data was derived from an RCT by the Cooperative Group in 1988 addressing the same question. In 41 treated patients and 40 controls, the main effect demonstrated after 1 year was a reduction in infections; 23 in treated group and 41 in placebo group (see preceding chapter for further details). No effects on survival were demonstrated, although the RCT was not powered to assess this. The only benefit considered in the base-case of the model was thus reduced infections and reduced costs arising from this. The costs in the model were derived from cost data from two Boston teaching hospitals in 1989 US $. For instance the cost of a major infection requiring hospital admission was estimated as $5,149, the basis of which is presented in an Appendix to the paper. The estimated annual cost of IgRT was $15,470, which includes costs of administration. Estimates were also made of the value to the patient of improved quality of life resulting from reduced infections. A panel of 10 physicians was asked to perform “reference gambles” to assess the relative value (utility) of each of the following health states:

- CLL without infection (mean 0.87; low 0.5; high 0.999)
- CLL with trivial infection (mean 0.86; low 0.5; high 0.999)

- CLL with moderate infection (mean 0.81; low 0.5; high 0.99)
- CLL with major infection (mean 0.46; low 0.2; high 0.90)
- Intravenous immunoglobulin infusion (mean 0.66; low 0.2; high 0.99)

The decrease in quality of life associated with 17 days of IVIg infusion was not incorporated into the base case model, but was included in the sensitivity analysis. The sensitivity analyses also considered how cost-utility would alter if a survival gain were assumed, if the impact on numbers of infections were greater, if the utility gain associated with avoiding an infection were greater and if cost IgRT were reduced.

The resulting cost-utility estimate was $6 million per QALY. Varying assumptions individually made little difference to this unfavourable ICER. The ICER did fall to $34,400, when the following four assumptions were made:

- 50% reduction in one year mortality
- probability of remaining infection free was 50% higher than observed in RCT
- utilities associated with infection were 50% lower than those used in the base case
- 50% reduction in cost

The authors of the paper felt this combination of possibilities was implausible however and so concluded that IgRT in CLL was not cost-effective

6.2.8 Summary of main findings of systematic review - PID

SCIg vs No IgRT

- Although open to bias, the QoL literature offered the only insight into the size of the effect associated with use of SCIg

- The observation based on these four studies suggests improvement in QoL and reductions in doctors visits and hospitalisations is associated with use of IgRT

IMIg vs IVIg

- IVIg is more expensive than IMIg
- The increase in costs appear to be completely offset by reduction in antibiotic use and reduced numbers of days of hospitalisation
- The validity of this observation is reduced by total absence of information on the data which was used to calculate the costs

IVIg vs SCIg

- There is an apparent clear difference in cost between IVIg and SCIg
- This is undermined to some degree by shortcomings in the cost-minimisation approaches used; these shortcomings seem unlikely to completely account for the lower costs for SCIg
- The main driver of the difference is the unit costs of IVIg and SCIg, and there are some reasons to suggest that the disparity in unit costs in the German study may no longer apply in the UK
- It should be noted that even if IVIg or SCIg is found to be preferable in terms of cost (or effectiveness), there may be over-riding reasons for using one or other preparation e.g. unable to achieve IV access or previous anaphylactic reactions with SCIg
- Changing from hospital IVIg to home SCIg is appears to be associated with improved QoL and treatment satisfaction. How much of this is due to change in route of administration and how much to the setting in which the treatment is done is unknown however. A study comparing hospital based to home-based IVIg would be required to make such an assessment.

General

- IVIg treated PID does not return health-related quality of life to normal levels

6.2.9 Summary of main findings of systematic review – CLL

- The decision-analysis by Weeks et al was generally well conducted, and its conclusion concerning IgRT not being cost-effective appears robust
- This conclusion is unlikely to be generalisable to IgRT in PID because:
  1) Level of Ig deficiency is greater – impact on infection reduction likely to be greater
  2) Patients are much younger
  3) Sequelae of repeated infection esp bronchiectasis highly likely in PID; unlikely in CLL
  4) Impact on mortality plausible in PID; less likely in CLL

6.2.10 Implications for further components of health economic evaluation

Although the existing economic evaluation of IVIg for CLL is open to criticism and could be improved, it was felt that the priority was to focus on the cost-effectiveness of IVIg for PID. Recommendations for the cost-effectiveness of IVIg for CLL thus rest on the evidence on effectiveness systematically reviewed in the previous section and the published model of cost-effectiveness.

Concerning the cost-effectiveness of IgRT for PID two questions were felt to be of particular importance:

a) What is the cost-effectiveness of IgRT relative to no treatment in PID
b) What is the cost-effectiveness of SCIg relative to IVIg

The first of these questions has not been directly addressed before, so the main means to estimate the cost-effectiveness of IgRT could only be through economic modeling, if further primary research could not be conducted. The first element of the further economic evaluation was thus to examine the feasibility of such a model. The second element was to investigate whether estimates for key model parameters were available, particularly impact on mortality, which had not been measured in any RCTs identified. The second question on cost-effectiveness of SCIg vs IVIg had been previously addressed in an economic evaluation, but in a non-UK setting. The third element of the further economic evaluation was thus to examine whether the results were applicable in the UK. This component of the further economic evaluation also served to identify UK-based cost information for the prospective model of the cost-effectiveness of IgRT versus no treatment. The final component of the further economic evaluation was to be delivery of the economic model, should it prove feasible.

6.3 Feasibility of a health economic model of the cost-effectiveness of IgRT versus no IgRT in PID

Understanding the nature of PID and the systematic review of effectiveness we identified the following as the areas where IgRT is likely to exert most of its benefit:

- Reduction in infections
    - Reduced number
    - Reduced severity
    - Improved quality of life during period of infection
    - Reduced health service costs
- Reduced chronic infection
    - Damage to body organs as a result of repeated infection especially to lungs (bronchiectasis)
    - Organ failure especially respiratory failure

- Reduced mortality

The areas of potential disbenefit associated with IgRT are:

- Infections transmitted by IgRT
- Virus contaminant
- Adverse reactions to IgRT
    - Most severe – anaphylactic reactions
    - Local reactions
- Reduction in quality of life associated with regular administration of IgRT

The critical costs from a health service perspective are:

- Cost of IgRT
- Cost of administration
- Avoidance of costs associated with treatment of infection

Costs to the patient, their family and society should also be considered. As with many chronic diseases a treatment which allows patients or their families to lead more economically active lives may be very influential in any assessment of the relation between benefit and cost from a societal perspective.

Any economic model must attempt to capture the above. The diagram below illustrates how this might be achieved. A Markov model is proposed to capture the recurring nature of infections in particular. There are seven states, infection being sub-divided into three separate states based on the degree of severity (minor infection requires visit to GP alone; moderate infection requires treatment in community; severe infection requires admission to hospital). The arrows indicate how patients may move from one state to the next. Thus in a given time period someone with PID may either remain stable (re-circulating arrow), develop infection (and recover from it), or develop bronchiectasis (or other chronic infective complication) or die from a non infective cause. The dotted arrow from PID with bronchiectasis to PID indicates that reversion from the chronic infection state is unlikely – a heart lung transplantation would be the means by which this

could be achieved therapeutically. The model would be used to compare the outcomes and costs with IgRT with those without IgRT. The effect of a proportion of patients suffering adverse events at average rates over the time period in question would be incorporated.

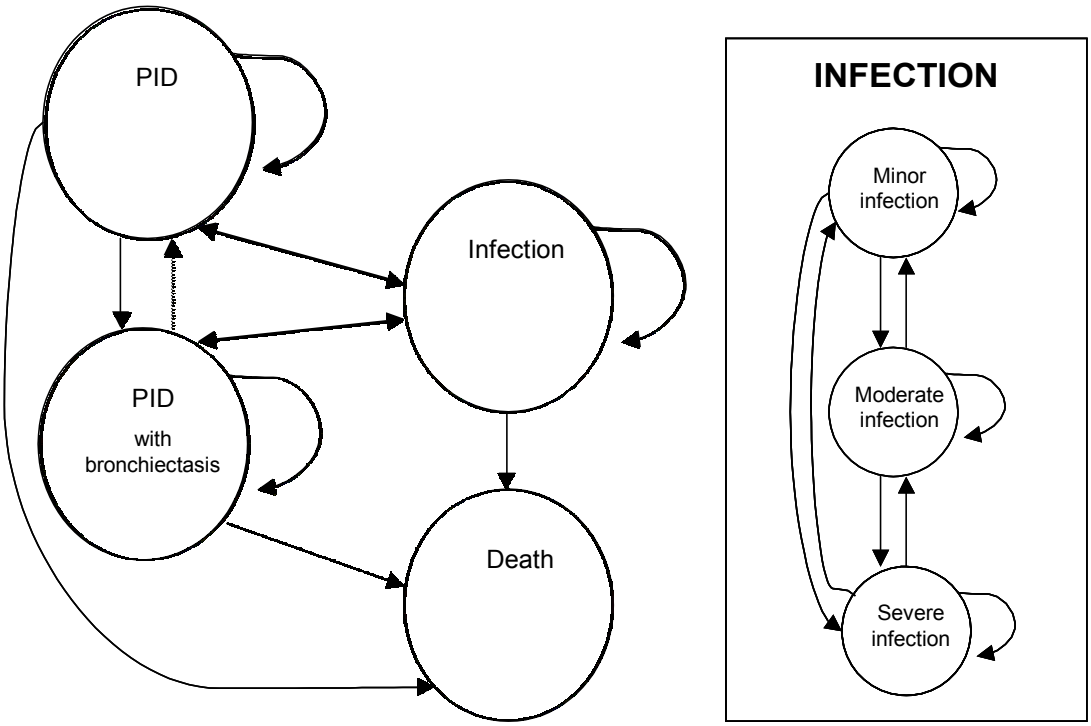


Figure 1. Full model

This is a complex model for which the main limitation would be availability of data for both IgRT treated *and* untreated patients. The fact that there are no RCTs comparing IgRT with placebo adds to the handicap. Scant pre-post data was identified giving an impression of the impact of SCIg relative to no treatment in terms of infections and health-related quality of life. Although a very crude approximation, the data on impact on infections could be corroborated using comparisons between IMIg and IVIg, acknowledging that this would be an under-estimate of effectiveness as IMIg is likely to have some efficacy. However, although estimates of impact on infections and health-related quality of life seem to be available, there was no data on impact on mortality. The absence of such thus emerged as the main barrier to progressing with a model, and seeking such was the main focus of the next element of the economic evaluation.

6.4 Estimating the impact of IgRT on mortality in PID

All searches, particularly those to identify literature for the systematic review of economic evaluations were reexamined for any data on mortality. Two studies were identified with survival data:

- Cunningham-Rundles and Bodian 1999[53] providing an estimate of survival on current IgRT regimes
- MRC study 1971[56] providing and estimate of survival with early low dose IMIg, used as proxy for untreated survival rates.

Cunningham-Rundles and Bodian presented the results of follow-up of all subjects with the main type of PID, common variable immunodeficiency (CVI), presenting to or diagnosed by the Immunodeficiency Clinic at the Mount Sinai Medical Centre from 1973 to 1998. This comprised 248 patients with an age range 3 to 79. The vast majority of the patients received IVIg throughout the period of observation. There were 102 males and 146 females. The median age at presentation was 23 years for males and 28 years for females. The following groups of patients were not included:

- Children under 2 years who had no further follow-up history to confirm continued hypogammaglobulinaemia
- Patients with known X-linked (XLA, Bruton-type) agammaglobulinaemia
- Hypogammaglobulinaemia with thymoma
- Immunoglobulin deficiency due to secondary loss ie through intestinal loss

Follow-up information from those no longer receiving care at the Mount Sinai Medical Centre was sought from the patients and/or the patient's physician. For those who had died the cause of death was determined by review of death certificate, autopsy report and/or contacting the attending physician. Probabilities of survival after diagnosis of CVI were estimated from Kaplan-Meier life tables. These were compared with the expected survival in the general population

based on age and sex-matched US mortality rates for 1990. Survival time for the CVI patients was measured from age at diagnosis to death or the last contact with the patient. By 1998 57 patients had died, 153 were known to be alive and 38 could not be located. The median follow-up period was 7 years (range 0 to 25). The 57 deaths occurred 1 to 32 years after diagnosis. The mean age at death was 40 years for males and 45.5 years for females. The full survival curves for the CVI cohort and the age-sex matched US cohort, separated into males and females are presented in the figure below. The most obvious feature is that survival is markedly worse for the CVI cohorts. The 10 and 20 yr survivals are:

- 10 yr (read from graph)
    - Male; US general 97%
    - Male; CVI 78%
    - Female; US general 98%
    - Female; CVI 78%
- 20 yr (taken from text)
    - Male; US general 92%
    - Male; CVI 64%
    - Female; US general 94%
    - Female; CVI 67%

The two main single causes of death were lymphoma, 10 cases and chronic lung infections resulting in cor pulmonale, 6 cases. However, chronic lung damage was almost certainly involved in 7 other deaths described as “respiratory insufficiency, malnutrition” and “post lung transplant, chronic or acute rejection”.

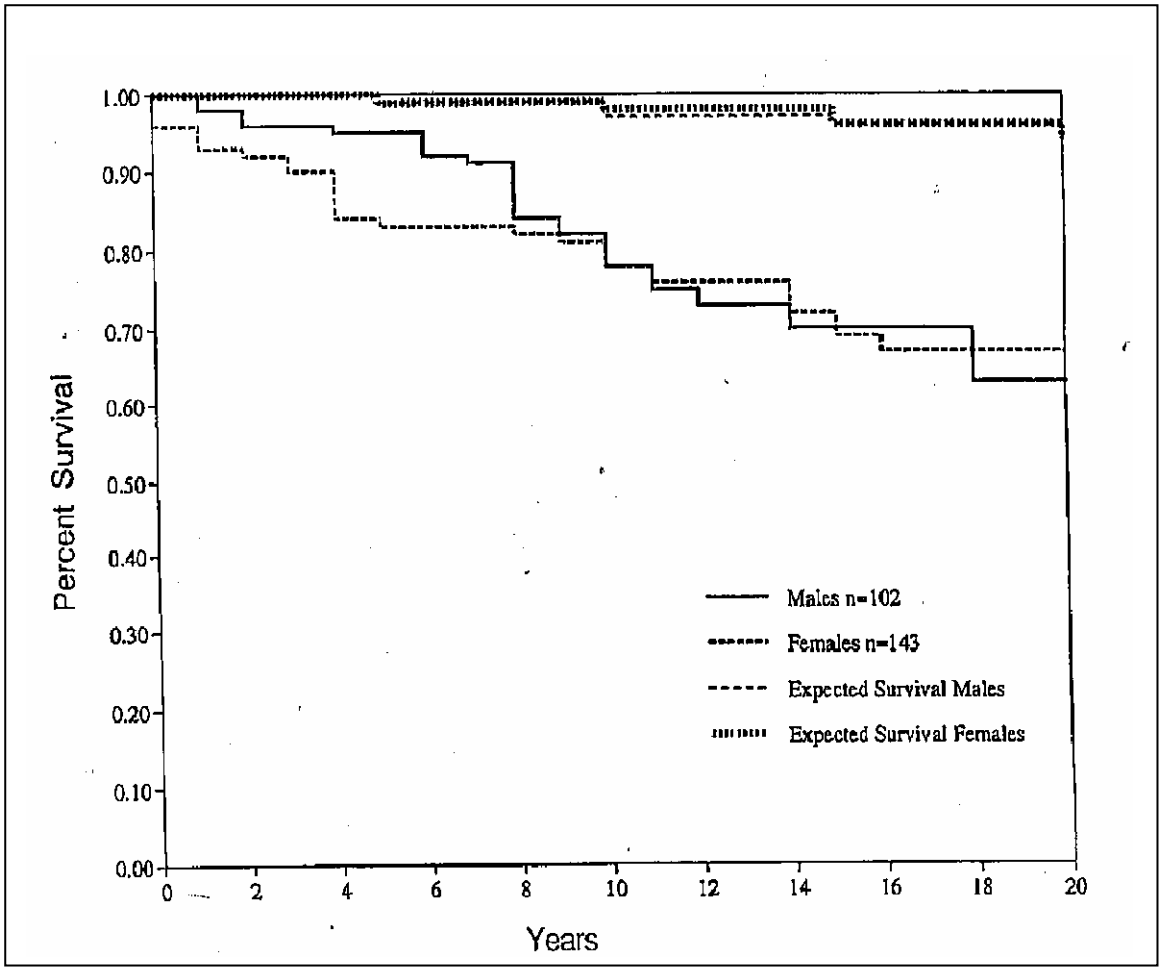


Figure 4.
Cunningham-Rundles & Bodian 1999

Commenced in 1955, the MRC study's main aims were to compare the effectiveness of different doses of IMIg and to collect information on the natural history of hypogammaglobulinaemia. The rationale was that as the study was the main source of exogenous immunoglobulin injections, then newly identified as a potential treatment for hypogammaglobulinaemia in the US, the study would capture nearly all the cases of hypogammaglobulinaemia occurring in the UK over the course of study, which ran until December 1966. 184 patients were admitted to the study (8 subsequently excluded as not actually meeting the entry criteria) and a further 24 patients were confirmed as meeting the entry criteria, but did not receive treatment as part of the study. The entry criterion was a serum immunoglobulin level of 200mg/dl or less (or 100mg/dl or less for infants

under 6 months of age). The doses of IMIg given to the patients varied over the course of the study were:

Initial series, X & Y: 0.025g/kg/wk or 0.05g/kg/wk (4 month cycles)
Series E & F: 0.01g/kg/wk or 0.05g/kg/wk
Series P & Q: 0.025g/kg/wk or 0.05g/kg/wk (1 year cycles)

Even the highest of the doses 50mg/kg/wk, equivalent to 150mg/kg/month, is at least half the current accepted dose (400-600mg/kg/month), and this assumes that the bioavailability of IMIg is similar to IVIg and SCIg and that the preparations being used in the 50's and 60's were as biologically active as current preparations. The fact that doses were indeed low by today's standards is confirmed by serum Ig levels achieved during the study being relatively low – 0.01g/kg/wk achieved levels of about 150 mg/100ml; 0.025g/kg/wk achieved levels of about 230 mg/100ml; and 0.05g/kg/wk achieved levels of about 340 mg/100ml. Current target levels would be at least twice these. It was on these bases that the MRC study was felt to be a cohort which best represented untreated PID. In comparions it must however be continually remembered that the "untreated" cohort are actually receiving IgRT.

The MRC study identified 51 deaths in the 176 persons included in the study, giving a crude mortality rate of 29%. 40 of these deaths occurred while the patients were receiving IgRT as part of a trial schedule; 1 of these before treatment could be commenced; 11 further deaths occurred in patients (14 in total) who had withdrawn from the treatment regimen but continued to receive IgRT, often at a higher dose. Of the 40 deaths occurring while the patients were receiving IgRT as part of a trial schedule, 26 occurred within 6 months of diagnosis and 14 after. Those under 1 year of age suffered 15 of the 26 deaths within 6 months of diagnosis; the 15 deaths occurred in 33 cases under 1 year (crude rate 45%). This mortality information, although extremely valuable, cannot be compared directly with that presented by Cunningham-Rundles and Bodian. The MRC study does however provide complete anonymised case histories of all

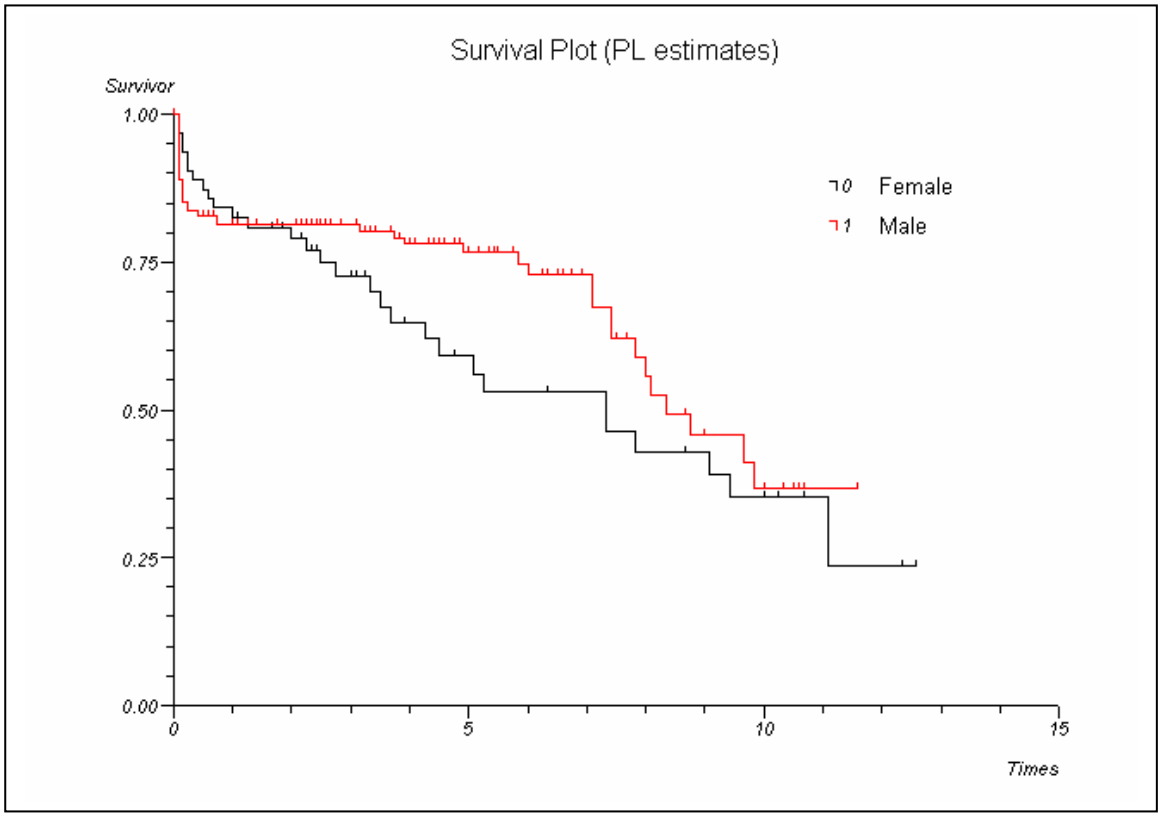
patients in the study (177) and those who were eligible but not entered into the study (24)[‡]. Working from these case-histories one of the reviewers (CH) identified the time in years and months, from diagnosis (date serum Ig level <200mg/100mls or date IgRT commenced) to either death or the date of last contact. Where the contact was only given as a year, it was taken to be December of that year. The resulting survival times were analysed as a Kaplan- Meier plot (using StatsDirect software). This is presented in the Figure below.

This indicates that 10 year survivals are:

- Male – 38%
- Female – 36%

Restricting the analysis to just those entered into the study (n=177) makes no difference to the 10 year survival. Excluding the study participants less than 1 year improves 10 year survival to 47% in males and 38% in females.

[‡] Unclear why there are 201 case histories, but the total number of patients generally described by the MRC study report is 176 (eligible and in study) + 24 (eligible but not in study) = 200



The survival curves for the two studies are clearly different, mortality being markedly worse in the MRC study. However, great care needs to be exercised in automatically attributing the difference to IgRT. The following also needs to be considered:

a) differences in the nature of the populations; this seems likely as the New York cohort is restricted to CVI, whereas the MRC trial population is a heterogenous mixture of all causes of hypogammaglobulinaemia
b) differences in the ascertainment/diagnosis of cases in each study
c) differences in treatment between the New York and MRC trial, other than IgRT, particular supportive antibiotic treatment
d) that the MRC trial is not a truly untreated population, as IMIg was given to most people in the study

How these potential confounding factors affect a judgement as to how much of the difference in survival is attributable to introduction of IgRT, or indeed whether

it is an underestimate, is a matter of speculation. The most valid measure of such would be an RCT with survival as the primary outcome, but this study could no longer be mounted – indeed a placebo-controlled study was felt to be unethical even at the time when the MRC study was commenced in 1955. Non experimental approaches (cohort analyses of existing data) might provide further information on the effect of treatment on mortality, but this assumes historical data of adequate quality exists and funding to undertake considerable further analysis would be available. Thus, particularly in the context of this report, and probably generally, although subject to high levels of uncertainty the difference in survival between the New York population and the MRC study population provides the only current estimate of the effect on survival attributable to IgRT. Ignoring possible effects on survival in modeling the cost-effectiveness of IgRT would be another possible approach to dealing with the observed uncertainty. Unfortunately, the credibility of any cost-effectiveness estimates, particularly if unfavourable, which failed to consider mortality would be low. Thus if calculating the cost-effectiveness of IgRT is thought to be important, some attempt to estimate the impact on survival is inevitable.

6.5 Examining the applicability of published IgRT cost estimates to the UK

Two studies were identified assessing the cost-effectiveness of SCIg relative to IVIg. Both assumed equal effectiveness and adopted cost-minimisation approaches, on which basis both concluded that SCIg at home cost less than IVIg in hospital, and so that SCIg was more cost-effective. As neither study was done in the UK, the third element of the further economic evaluation considered whether the assumptions used in the most recent paper by Hogy et al[45,46] applied in the UK. Ideally we would have repeated the costing processes from scratch. This was however beyond the scope of the report. We thus asked a well established clinical immunology service (John Radcliffe Hospital, Oxford) to consider whether the costs identified by Hogy et al paper were applicable, and if not, what more appropriate alternative costings representative of UK practice

might be. The results of this exercise are presented as a Table below (**Table 63**). The UK £ 2005 equivalent costs were obtained by converting €2003 to £2003 using the mean of the monthly conversion rates (1.453) recorded at http://www.uktradeinfo.com, and inflating £2003 to £2005 using an annual inflation rate of 2.9% [http://www.pssru.ac.uk/pdf/uc2004/uc2004_inflation.pdf accessed 28/10/05]

Table 63: Appropriateness of Hogy et al base case assumptions to the UK

	Base case assumption	UK £ 2005 equivalent of Hogy et al costs	Comments/ alternative values more appropriate for UK
Weight adult	75kg	N/A	Reasonable; 70kg is more often used as standard adult weight
Weight child	40kg	N/A	
Monthly dose Ig	0.4g/kg	N/A	0.4g/kg/month reasonable; up to 0.6g/kg/month possible. Monthly dose is same for SCIg and IVIg. Dosing interval tends to be 3 weeks for IVIg; and 1 week for SCIg
Price/g IVIg	€84.60	£61.65	Too high Current UK list price £31.06/g (Sandoglobulin®) or £26.74/g (Octagam®). Use £30/g
Price/g SCIg	€38.54	£28.09	About right UK list price £37.00/g but discounted (Vivaglobin®; Subcuvia®). Use £30/g
Premedication adult (IVIg only)	€11.21	£8.17	Not routinely used in UK, so zero cost more appropriate. Only used regularly with first two iv infusions in UK.
Premedication child (IVIg only)	€6.41	£4.67	
Yearly cost SCIg pump	€154.74	£112.76	Possibly low. Standard pump in UK costs £900 (compared with €773.72 claimed). Pump life is probably considerably longer than the 5 years claimed by Hogy et al. However, each patient recommended to have two pumps. Suggest £180 per annum
Yearly cost SCIg infusion materials	€620.31	£452.04	Reasonable. UK unit questioned uses home delivery service to provide consumables; charge £150/quarter
Yearly cost IVIg infusion materials	Not included		Unclear why no cost included. Even though IVIg is given less frequently the cost of consumables is greater. UK unit questioned uses same home delivery service to provide consumables; charge £150/quarter
Treatment/ diagnostic procedures IVIg (per year)	€559.48	£407.71	Too high. Costs of monitoring would be similar to SCIg as most IVIg is given at home in contrast to assumption operating in Hogy et al that IVIg is given as hospital O-P
Treatment/ diagnostic procedures SCIg (per year)	€243.87	£177.71	Reasonable. Patients would be reviewed by medical staff twice annually. In addition costs of monitoring serum Ig need to be included, as does cost of annual blood test for HCV
Sick leave for caregivers IVIg (per year)	€520	£378.94	This is a specific reimbursement for parents in Germany not received in the UK. However even considering the impact on parents' time, in the UK there would be little difference in "cost" between IVIg and SCIg because both are given at home
Sick leave for caregivers SCIg (per year)	€240	£174.89	

Notes: Ig = Immunoglobulin; IVIg = Intravenous Ig; SCIg = Subcutaneous Ig

Table 64: Applying more appropriate UK assumptions to Hogy et al's cost calculations for adults (IVIg and SCIg given at home)

Costs per year – UK £2005	**Adult - as per Hogy et al**		**Adults – revised to take UK context into account**	
Item	IVIg	SCIg	IVIg	SCIg
Medication				
• Ig	22,194	10,110	10,800	10,800
• Premed	8	0	0	0
SCIg infusion pump	0	113	0	180
Infusion materials	0	452	600	600
Treatment/diagnostic procedures	407	178	180	180
Sick leave for caregivers	0	0	0	0
Total	**22,609**	**10,853**	**11,580**	**11,760**

Table 65: Applying more appropriate UK assumptions to Hogy et al's cost calculations for children (IVIg and SCIg given at home)

Costs per year – UK £2005	Children – as per Hogy et al		Children – revised to take UK context into account	
Item	IVIg	SCIg	IVIg	SCIg
Medication				
• Ig	11,837	5,393	5,760	5,760
• Premed	4	0	0	0
SCIg infusion pump	0	113	0	180
Infusion materials	0	452	600	600
Treatment/diagnostic procedures	407	178	180	180
Sick leave for caregivers	379	175	0	0
Total	**12,627**	**6,310**	**6,540**	**6,720**

Re-consideration of the costs thus suggests that there are important differences between those applied by Hogy et al and the situation in the UK at present. These differences partly arise from the assumption that IVIg treatment inevitably involves treatment in hospital. In the UK this no longer appears to universally be the case, and certainly not at the unit providing information on cost. Where IVIg and SCIg are both given at home, the cost of the immunoglobulin is the main driver of overall cost. The finding that UK unit costs of SCIg and IVIg are much more equal than those used by Hogy et al is highly influential, challenging previous conclusions by Hogy et al and Gardulf et al that SCIg is more cost-effective. Indeed judged on UK list prices alone, SCIg may actually be less cost-

effective. The reality however is that market forces are currently keeping SCIg and IVIg unit costs similar. Thus, if outcomes are indeed equivalent, neither IVIg nor SCIg has an advantage in terms of cost-effectiveness where both are given at home.

Where IVIg is given in hospital and SCIg at home, the charge by NHS hospital trusts to commissioners must be taken into account. Again it is not clear how Hogy et al incorporate these charges or their equivalent in the German system into their costing. It is possible that they are part of the treatment/diagnostic procedures category, but the size of the charges seems too low for this to be the explanation. We thus used the revised UK estimates as the starting point for considering whether IVIg being given in hospital, rather than at home would make a difference to relative costs.

Table 66: Applying more appropriate UK assumptions to Hogy et al's cost calculations for adults; comparing IVIg and SCIg given at home with IVIg given in hospital and SCIg at home

Costs per year – UK £2005	**Adults - taking UK context into account (IVIg at home)**		**Adults – taking UK context into account (IVIg in hospital)**		**Comments**
Item	IVIg (home)	SCIg (home)	IVIg (hosp)	SCIg (home)	
Medication					
• Ig	10,800	10,800	10,800	10,800	
• Premed	0	0	0	0	
SCIg infusion pump	0	180	0	180	
Infusion materials	600	600	0	600	Assume iv infusion materials are covered in hospital charge
Treatment/diagnostic procedures	180	180	0	180	Assume O-P attendances are covered in hospital charge
Sick leave for caregivers	0	0	0	0	
Hospital charges	N/A	N/A	7,800	N/A	Assume charge based on day-case rates (c £450). Infusions every 3 weeks
Total	**11,580**	**11,760**	**18,600**	**11,760**	

This analysis demonstrates that giving IVIg in hospital greatly inflates the costs of IgRT from the health service perspective, and re-establishes SCIg at home as

the more cost-effective option. However, whereas the analysis by Hogy et al suggests this is due to differences in IgRT preparation costs, in the UK the difference is due to hospital charges. Thus in the UK any difference in cost-effectiveness is mediated by the setting (home being more cost-effective than hospital), not the preparation. It is worth noting that this assumes that hospital IVIg and home SCIg are equally effective, and that the RCT by Chapel 2000 compares IVIg with SCIg in the hospital setting. Whether changing the setting of infusion alone alters effectiveness has not been rigorously assessed but the quality of life study by Gardulf et al 2004 (see section 6.2.6) suggests that there may be improvements.

6.6 Simple model of cost-effectiveness of IgRT vs no IgRT

Although it was immediately apparent that the full model envisaged to address the question of cost-effectiveness of IgRT vs no IgRT was not feasible, the emergence of some data, however imperfect on impact on mortality, suggested that a simpler model might be feasible. The three state Markov model illustrated below was designed and run using an Excel spreadsheet. The cycle length was 1 year and the model was run over 10 years. A health service perspective was adopted to make it comparable with most other health economic evaluations of health care interventions, and the currency/cost year was 2005 UK £.

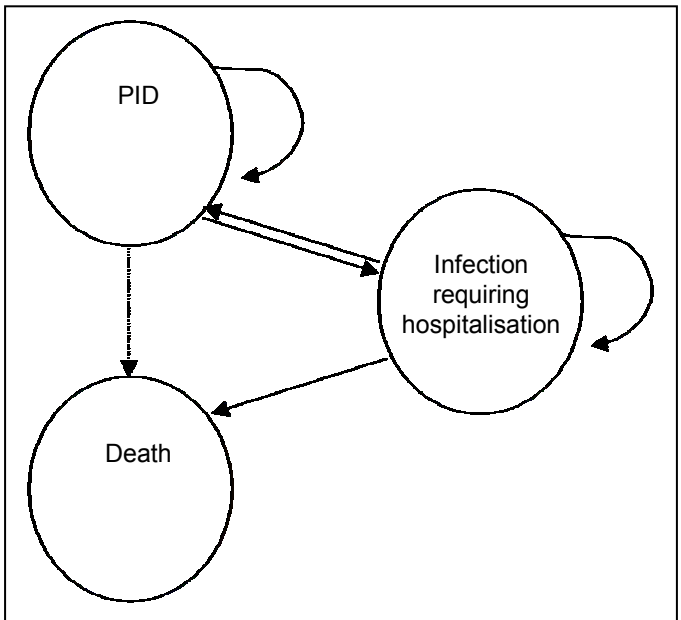


Figure 2. Simplified model

Before considering how the model was populated, the limits of the available data and the results, the implications of departing from the ideal model must first be considered. The most important of these are:

- that any benefits associated with avoidance of infections not serious enough to require admission to hospital are no longer captured
- benefits associated with potential reduction in chronic infection, particularly of the lungs, are no longer captured
- disbenefits associated with rare but serious infections transmitted by IgRT are not considered

Given that the latter is currently a largely theoretical risk (emergence of a new infectious agent which is not inactivated by current IgRT preparation processes), on balance the simpler model is likely to underestimate the cost-effectiveness of IgRT.

Finally it should also be noted that the model does not distinguish between deaths occurring independently of infection (which might not be expected to be influenced by IgRT) and those as a direct consequence of infection. It is for this reason that the arrow between PID and death is dotted.

The table below indicates the parameters for the base-case model and their sources

Parameter	**IgRT**	**No IgRT**	**Sources**
Survival (assume deaths occur mid-year)	2.4% per annum (equivalent to 10 yr survival rate of 78%)	9.5% per annum (equivalent to 10 yr survival rate of 37%)	IgRT – Cunningham-Rundles and Bodian No IgRT – MRC study
Utility of survival (on days when not hospitalized with infection)	0.8	0.8	Estimates informed generally by HRQoL literature
Rates of hospital	10% of rates with	5.7 days per	IgRT – Galli et al

infection (applied to all those alive at start of any year)	no IgRT	patient per year	1990 No IgRT – Gardulf et al 1993
Cost of infection	£285 per day		NHS reference costs 2004
Utility of infection	0.46		Weeks et al
Weight of patient	70kg		Standard
IgRT dose	N/A	0.4g/kg/month	Product characteristics
IgRT cost	N/A	£30	UK list price for IVIg
Discount rate, costs	6% per annum		Current NICE recommendations
Discount rate, benefits	1.5% per annum		
Notes: Shaded cells indicate parameters where IMIg is used as a proxy for no IgRT			

Some assumptions were required to derive the parameters listed. The most important was that two of the estimates, indicated by shaded cells, were based on results from IMIg treated patients being used as a proxy for no IgRT. The general concerns about the basis of the survival estimates have already been discussed at length, and should be further re-emphasised, particularly the likelihood that any comparison between the two survival rates is subject to confounding. It should also be noted that applying a fixed annual mortality rate does not lead to a perfect match between the modelled and actual survival curves, although this affects each arm equally. The 10 year survival rates do precisely coincide, however the imprecision (95%CI) around each estimate is not taken into account. The utility estimates are the parameters with least evidential base. Although there is useful information about the health related quality of life in IgRT treated patients, utilities have never been measured directly. The value of 0.8 for IgRT reflects considerable disruption of life associated with administration of IgRT (now much reduced with home-based treatment) and occasional adverse events (fortunately rare with modern IgRT preparations). Such disruption does not affect the no IgRT patients in the model, but would be substituted by other phenomena likely to erode utility such as low level infections and fear of infection. Whether the nett effect is equal leading to identical utility for

IgRT and no IgRT patients is highly speculative, but in the absence of firm information an assumption of no difference seems the most appropriate. The utility associated with hospital infection *is* based on direct utility elicitation, albeit in a small number of physicians considering the effect of severe infection in secondary immune deficiency in CLL.

There is also uncertainty about the cost of severe infection requiring hospitalisation. The estimates of average numbers of days of infection per patient in both IgRT and no IgRT groups was based on scant information. The number of days of infection experienced in untreated patients is based on data from 10 untreated patients during the 18 months phase prior to starting SCIg in the study by Gardulf et al 1993. The event rate in the IgRT group is based on a 90% reduction in hospital days observed in the study by Galli et al on 23 children switched from IMIg to IVIg. The costs per day are taken from 2004 NHS reference costs. There are however a number of different HRG codes representing the costs associated with the types of infection which might be experienced by patients with PID. D16, bronchiectasis was chosen – there were many other codes where daily costs were considerably higher. The costs of IgRT were derived from the second component of the further economic evaluation reported above. Standard weight was taken to be 70kg, as opposed to 75kg, on the basis that a substantial proportion of patients receiving IgRT will be children; monthly IgRT dose is well established and is the same for SCIg and IVIg; Ig cost/g was taken to be £30, as this is the UK list price for IVIg; the list price for SCIg is higher, but as already indicated competition keeps preparation costs similar. Discounting to below the £30/g list price for IVIg also occurs, however costs below £30 were only considered in the sensitivity analysis. Hospital charges that might be associated with IgRT given intravenously are not included in the base-case, but are considered in the sensitivity analysis (see below). Finally the future cost/benefits discounting rates were at the levels suggested by NICE. These are however under review with a suggestion that 3.5% pa for both costs and benefits may be more appropriate.

Using the above parameters the base-case cost-utility estimate was £30,168 per QALY as summarized in the table below:

	QALY	Cost (£ UK 2005)	ICER
IgRT	719.0	7,508,074	
No IgRT	500.1	904,339	
Difference	218.9	6,603,735	**£30,168**
Notes: Values are for 100 persons over 10 years ICER – Incremental cost-effectiveness ratio			

To examine the effect of variation in the model parameters one-way sensitivity analyses were done. The focus was on giving an indication of the influence of parameters on the ICER qualitatively i.e. did increasing days of infection increase or decrease cost-effectiveness. Normally it would be hoped to indicate a plausible range of values between which the true ICER might lie; this was not felt to be an appropriate goal in this economic model because the amount of information about many of the parameters was so limited. The results of the sensitivity analyses are indicated in **Table 67** below:

Table 67: Results of one-way sensitivity analyses

	Change in parameters	ICER (Cost/QALY)	↑↓
Base-case		£30,000	
Increase survival benefit associated with IgRT	No IgRT mortality rate 9.5% to 12%, IgRT remains 2.4% per annum	£24,000	↑
Decrease survival benefit associated with IgRT	No IgRT mortality rate 9.5% to 7%; IgRT remains 2.4% per annum	£42,000	↓↓
Worsen utility associated with PID if not seriously infected	Utility 0.8 to 0.7 for both IgRT and no IgRT groups	£35,000	↓
Utility associated with PID better for IgRT than no IgRT	Utility 0.8 to 0.9 for IgRT; utility for no IgRT still 0.8	£27,000	↑
Utility associated with PID worse for IgRT than no IgRT	Utility 0.8 to 0.7 for IgRT; utility for no IgRT still 0.8	£51,000	↓↓
Severe infection more common in both IgRT and no IgRT groups	Days of hospitalization changed from 5.7 to 11.4 per patient per year	£26,000	↑
Severe infection less common in both IgRT and no IgRT groups	Days of hospitalization changed from 5.7 to 2.3 per patient per year	£33,000	↓
Effect of IgRT on severe infection greater	Rates of infection in IgRT changed from 10% to 5%	£30,000	↑
Effect of IgRT on severe infection less	Rates of infection in IgRT changed from 10% to 20%	£31,000	↓
Increase cost/day of infection	Change £285 to £480	£28,000	↑

Reduce utility associated with hospital infection	Change 0.46 to 0.30	£30,000	↑
Increase dose	Change 0.4/g/month to 0.6/g/month	£47,000	↓↓
Decrease Ig price	Change £30/g to £20/g	£19,000	↑↑
Increase Ig price	Change £30/g to £40/g	£41,000	↓↓
Include hospital charges where IVIg can only be given as O-P	Include day-case charge @ £450 per infusion	£56,000	↓↓
Discounting costs and benefits at 3.5% per annum	Base-case Costs 6%; benefits 1.5%	£38,000	↓
Discounting costs and benefits at 6% per annum	Base-case Costs 6%; benefits 1.5%	£40,000	↓
No discounting	Base-case Costs 6%; benefits 1.5%	£36,000	↓
Notes: ↓ Worsened cost-effectiveness – increased costs relative to the effects ↓↓ Markedly worsened cost-effectiveness ↑ Improved cost-effectiveness – reduced costs relative to the effects ↑↑ Markedly improved cost-effectiveness			

The sensitivity analysis indicates that the base-case ICER is sensitive to changes in assumptions concerning the parameters. All the alternative values suggested are within plausible ranges for the parameters, such is the uncertainty concerning the values. The parameters which seem to have a particular influence on the base-case ICER are:

- Estimates of the survival benefit associated with IgRT. Reductions in the survival benefit seem to have a marked unfavourable impact on cost-QALY. This would be true irrespective of whether the reduction in survival benefit were achieved by decreasing the annual mortality rate in the no IgRT group (as in the table), or increasing it in the IgRT group
- The model seems to be highly sensitive to assumptions about the utility assigned to patients who are not being affected by infection requiring hospitalization – the day-to-day utility of survivors in the IgRT and no IgRT group. The change with the most marked effect on the ICER is if the utility in the IgRT survivors is reduced to less than that in the no IgRT survivors. This would be the case if the inconvenience of giving IgRT and adverse events associated with IgRT outweighed any improvement in general well-being associated with IgRT. This scenario, seems however to be the less likely

option than IgRT actually being associated with improved utility relative to no IgRT

- Finally, as would be predicted, cost of immunoglobulin whether by altering unit cost or assuming dosing at the uppermost end of the dosing range, has marked effects of the ICER. Similarly introducing a hospital charge for infusion of IVIg in hospital has a marked adverse effect on cost-effectiveness.

Overall the simplified health economic model suggests that IgRT is cost-effective. The base-case ICER of £30,000, is at an acceptable level of cost-effectiveness, particularly in the context of a life-threatening disease. Although the model is tentative and there is enormous uncertainty surrounding the parameters, taking the ICER into values which would not be considered cost-effective, the assessment that the intervention is cost-effective is probably robust. This is firstly because the simplified model structure appears slightly biased against IgRT, because improvements in infections which do not result in hospitalization are not considered. The effect of this could be captured by improvement in day-to-day utility associated with IgRT, but this has so far not been measured directly as discussed above. Even with an adjustment to day-to-day utility any cost savings associated with reduced levels of infections not requiring hospitalization would not be captured. That the model is from a health service perspective, may also exclude benefits to the patient, carers and wider society, and these are likely to be favourable to IgRT, by allowing a greater degree of independence and ability to work and contribute economically. The second general consideration suggesting that on balance, despite the uncertainty, the results provided suggest IgRT is cost-effective is the fact that two sets of key parameters are based on the data where IMIg treated patients are taken as a proxy for no IgRT. Thus key estimates on impact on survival and impact on infections requiring hospitalization may have been underestimated.

Nontheless there is huge uncertainty and further work may reduce this. The most difficult to tackle would be improving estimates of impact on mortality, but even though an RCT may unachievable, corroboration of mortality experience in

recent cohorts of IgRT patients may be helpful. It may also be that long established databases or registers of PID patients may be re-examined to see whether there are cohort effects on mortality. Direct measure of utilities associated with treated IgRT would be helpful, as would greater accuracy of our assessment of the true costs of purchasing IgRT.

6.7 Overall conclusions on the cost-effectiveness of IgRT

The economic evaluation consisted of:

- Systematic review of past literature relating to costs, quality-of-life and cost-effectiveness of IgRT in both PID and CLL
- A more detailed analysis of the mortality effect and costs in using IgRT for PID
- Development of an economic model of the cost-effectiveness of IgRT for PID

6.7.1 IgRT for CLL

The key finding was of an existing economic model suggesting that IgRT is not cost-effective for CLL. The key parameters are derived from an RCT and the economic model was well conducted. Both counts suggest that the assessment is robust. Despite this some caution may be appropriate for the following reasons:

- The economic evaluation is relatively dated. Some of the assumptions which shaped the model 15 years ago, may have changed, particularly assessments about the levels of inconvenience and adverse events associated with IgRT
- The focus of the health economic evaluations in this report has been on PID rather than CLL

- Developing the model of cost-effectiveness for PID has inevitably offered insights which might improve the model by Weeks et al

However, against this caution is the extreme nature of the result by Weeks at al and the fact that a major effect operating in the cost-effectiveness of PID, survival benefit, is unlikely to be operating in IgRT in CLL. Morbidity associated with chronic infection, particularly of the lung, is also less likely to be operating too. Whether cost-effectiveness of a relatively high cost treatment can be sustained on the basis avoidance of infective complications is debatable, but it may be that there are sub-groups of patients with very high levels of infection without IgRT, where an argument for IgRT might be able to be made.

6.7.2 IgRT for PID

Although there is literature on costs and quality of life, in contrast to CLL there is no formal assessment of the cost-effectiveness of IgRT relative to no IgRT. The focus of the economic evaluations that do exist has been on the cost-effectiveness of SCIg relative to IVIg. The focus for the economic evaluation beyond the literature review in this report was thus to develop a better understanding of the relationship between cost and benefit concerning IgRT. Developing an economic model to assess cost-utility was the key step we have undertaken which has not been done before. Identifying information allowing us to quantify, albeit crudely, the mortality benefit associated with IgRT was a key step which made such a model feasible. We can only speculate on why this appears to be the first attempt to assess the cost-effectiveness of IgRT – the most likely explanation is that the treatment is well established and entered mainstream use at a time where costs were less of a constraint on new health service activity.

The key result is that the incremental cost-utility of IgRT relative to no IgRT is approximately £30,000. Assessment of the uncertainties associated with the

simple model structure, the perspective adopted, the estimates for the parameters and the sensitivity analysis indicate that there is considerable uncertainty about this ICER estimate. However, qualitatively at least there appear to be more reasons to suggest that the ICER estimates understate the cost-effectiveness of IgRT as over-state them. On this basis we are confident that IgRT is likely to be cost-effective. The sensitivity analyses indicate the parameters which if estimated inaccurately in our model would have greatest effect on the ICER. Estimation of mortality benefit is the parameter that we feel least confident about. However, a significant amount of uncertainty arises from the assessments of utility and cost too. Further research to improve the accuracy of these parameters may reduce uncertainty.

The other key results for the economic evaluation in this report concern the relative cost-effectiveness of SCIg and IVIg. The literature prior to this report strongly suggests that SCIg is more cost-effective, on the basis that SCIg is equally effective but at lower cost. The further analysis conducted as part of this report challenges these findings. In the UK at present there appear to be two facts underpinning this challenge:

a) The main determinant of IVIg/SCIg treatment, Ig price, no longer favours SCIg. Indeed according to current UK list prices, SCIg is more expensive.
b) Past comparsions of SCIg with IVIg are confounded by setting of treatment. In retrospect it is unclear how much of the advantage attributed to SCIg was actually due to home setting. The existing evidence that SCIg is superior needs to be considered in the light of the fact that in the UK at least, both SCIg and IVIg can be routinely given at home
c)

On balance we are thus confident that in terms of cost there should be little difference between SCIg and IVIg, unless IVIg is restricted to being given in hospital and charges levied. Any difference in cost-effectiveness must thus rest on difference in effectiveness, which the systematic review earlier in the report suggests is minimal. On balance we thus also conclude that the cost-

effectiveness of SCIg and IVIg are unlikely to differ significantly. Where IVIg is given in hospital and charges levied, SCIg at home remains the more cost-effective option. Whether cost-effectiveness should be judged on an apparently unnecessarily expensive model of care is debatable. There is clearly much uncertainty however, and further research on relative costs and effectiveness of SCIg in comparison with IVIg would be of assistance, particularly if it also helped reduce uncertainty about the cost-utility of IgRT vs no IgRT.

7. Overall report conclusions

7.1 Nature of report and its limitations

This report is a health technology assessment examining the effectiveness and cost-effectiveness of IgRT vs no IgRT, and IgRT of one type vs another type. The target conditions were PID and one specific cause of secondary immunodeficiency, CLL. The health technology assessment comprises a systematic review of effectiveness, a systematic review of economic literature and further economic evaluation principally involving development of an economic model to assess the cost-effectiveness of IgRT vs no IgRT in PID.

The main limitation of all parts of the report has been lack of relevant data. The results provided are subject to great uncertainty, both because data were not present, or where present, were subject to the effect of chance variation, bias and confounding.

There are however aspects of the methods we had to adopt which may have contributed to the uncertainty, or not reduced it to a minimum:

- The literature review, although systematic in approach, did not explore data beyond RCTs, qRCTs and crossover trials. It is possible that we may have overlooked data which may have improved the amount of evidence available to make assessments of effect, particularly in the context of the economic model
- The literature review did not explore the possibility of grey literature. In consequence we may have overlooked unpublished data, which may have had an important effect given the paucity of existing studies, particularly if publication bias was operating (unpublished studies tending to show less marked effects than published studies).
- Quantitative synthesis could not be applied owing to the small number of studies (often single) in each category of studies that could reasonably be combined. Even where more than one study did exist in a category,

difference in study design and/or difference in method of expressing a particular outcome further precluded meta-analysis. The effect has been that quantification of the size of effects has been difficult.

- In the economic evaluation the main limitation was resources. Just one researcher was available to undertake the systematic review of past literature on cost, quality of life and cost-effectiveness, and the further economic evaluations. Inevitably more detailed primary investigation of important issues such as cost was also precluded for the same reason, but such primary research would be unusual in HTAs.
- The limited resources available to develop the economic component of the report also affected the sophistication of the modelling approach adopted. However, we are less concerned about the effect of this because limitations in the available data were the main constraint concerning the modelling approach adopted.
- A major limitation, although stemming from lack of data already emphasised, is the inability of the economic model to fully take the patient and carer perspective into account. Although unsatisfactory in a chronic condition where the “cost” to the patient and their family are high, and can be greatly ameliorated by treatment, the disadvantage to the assessment of the cost-effectiveness of IgRT is likely to be minimal because so few economic evaluations, many involving other chronic conditions where the effect on patient and family are important, achieve this.

Concerning comparison with similar reports, we have not been able to identify anything equivalent. Clearly as indicated in the systematic review of past economic literature there have been some attempts to assess the relative cost-effectiveness of IVIg and SCIg. We do not agree with these assessments and have explained that the difference appears to arise from the different circumstances operating in the UK at the current time (as opposed to Germany (2003), & Sweden (1993)).

7.2 Main findings for effectiveness and cost-effectiveness

IgRT, particularly IVIg and SCIg, appears to be effective in terms of reduction of infection in both PID and CLL. The effect in PID appears to be greater, although no comparisons of IgRT with placebo or no treatment have ever been undertaken. The benefits of IgRT on infection appear to be off-set to some degree by adverse events, which are mild in nature. These reactions are said to have decreased over time, with newer preparations of IgRT. However, this point was not addressed in the systematic review. One study in Italy did identify HCV infection attributable to IgRT. Although no such similar event was reported in any other studies reviewed, the possibility of rare but serious infections not destroyed by current IgRT preparation methods is ever present, given that IgRT is a blood product. Beyond infection and adverse events, no rigorous data on outcomes such as mortality and rates of organ damage secondary to chronic infection were identified. Absence of such data is likely to be most important in the assessment of overall clinical effectiveness in PID, rather than CLL.

In PID, IgRT appears to be cost-effective, with a cost/QALY of £30,000 calculated in a newly developed Markov model comparing IgRT with no IgRT. This estimate is subject to considerable uncertainty and the assessment depends on evidence on effects on survival and utility that are not derived from RCTs. Other components of the economic evaluation suggest that the cost-effectiveness of SCIg and IVIg are likely to be similar, unless IVIg is only given in hospital and a charge for this levied. In this case SCIg at home remains more cost-effective in the UK at present, although the reason for this is not difference in IgRT preparation cost as indicated in past assessments of the relative cost-effectiveness of IVIG and SCIg.

In contrast, in CLL, IgRT is not cost-effective with an estimated ICER of approximately $6 million per QALY (US 1989). This is based on a well conducted decision-analytic model published 15 years ago. Although this study was based on effectiveness data from a well conducted placebo controlled RCT,

it is possible that the age of this assessment may be sufficient grounds for re-examining this model, which was not done in this report.

7.3 Implications for practice

There appear to be no major implications for practice.

The findings support continued use of IgRT in PID, but this is already well established. However, it does confirm the need to ensure that self-administered home infusions of IgRT are widely available, and this may not be universally available in the UK at present.

IgRT should not be extensively used in the treatment of patients with CLL. If audits suggest that IgRT is being used frequently in this situation, then this report suggests such activity is open to challenge.

7.4 Implications for research

There are implications for research. Improving estimates of the effect of IgRT on survival and utility in PID would be helpful, and need not require RCTs. It would require considerable additional analysis of existing data and presupposes these data sources still exist. Improving the assessments of the relative costs and effectiveness of SCIg vs IVIg, fully taking into account setting (home or hospital), would also be of assistance, particularly if this were used as an opportunity to collect data on utilities mentioned in the first research recommendation. Further development and testing of the new health economic model would also be helpful. Re-running the previously published health economic model on IgRT in CLL, might also be justified, particularly if it focused on cost-utility in groups with very high levels of infection.

Appendix 1

Clinical effectiveness
Search strategies

Database: Cochrane Library (Wiley) Internet version 2005 Issue 2

#1 primary next immunodeficienc*
#2 primary next immun* next deficienc*
#3 hypogammaglobulin?emia*
#4 agammaglobulin?emia*
#5 (immunoglobulin or antibody or gammaglobulin) next (deficienc* or defect*)
#6 CLL
#7 chronic next lymphocytic next leuk?emia
#8 exp Leukemia,Lymphocytic, Chronic/
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 (immunoglobulin* or antibody or gammaglobulin) next (replacement or infusion*)
#11 (intravenous or intramuscular or subcutaneous) next (immunoglobulin* or antibod* or gammaglobulin*)
#12 exp Immunoglobulins/
#13 #10 OR #11 OR #12
#14 #9 AND #13

Database: Ovid MEDLINE 1966 to March Week 5 2005
Search Strategy (Systematic reviews search) :

1 (immunoglobulin or antibody or gammaglobulin) adj1 (deficienc$ or defect$).mp.
2 secondary immunodeficienc$.tw.
3 (immunologic adj2 deficienc$).tw.
4 (impaired adj immune).mp.
5 (immune adj deficienc$).mp.
6 exp Immunologic Deficiency Syndromes/
7 or/1-6
8 (Ig adj replacement).mp.
9 (immunoglobulin adj replacement).mp.
10 intravenous immunoglobulin$.mp. or exp Immunoglobulins, Intravenous/
11 intramuscular immunoglobulin$.mp.
12 subcutaneous immunoglobulin$.mp.
13 (gammaglobulin adj infusion$).mp.
14 (immunoglobulin adj infusion$).mp.
15 exp Immunoglobulins/
16 or/8-15
17 7 and 16
18 (systematic adj review$).tw.
19 (data adj synthesis).tw.
20 (published adj studies).ab.

21 (data adj extraction).ab.
22 meta-analysis/
23 meta-analysis.ti.
24 comment.pt.
25 letter.pt.
26 editorial.pt.
27 animal/
28 human/
29 27 not (27 and 28)
30 17 not (24 or 25 or 26 or 29)
31 or/18-23
32 30 and 31
33 from 32 keep 1-9

Database: MEDLINE (Ovid) 1966 to April Week 3 2005
Search Strategy (RCTs search):

1 ((immunoglobulin or antibody or gammaglobulin) adj (deficienc$ or defect$)).mp.
2 hypogammaglobulin?emia.mp. or exp Agammaglobulinemia/
3 agammaglobulin?emia.mp. or exp AGAMMAGLOBULINEMIA/
4 primary immunodeficienc$.tw.
5 CLL.mp.
6 exp Leukemia, Lymphocytic, Chronic/ or chronic lymphocytic leuk?emia.mp.
7 or/1-6
8 ((immunoglobulin or antibody or gammaglobulin) adj (infusion$ or replacement$)).mp.
9 ((intravenous or intramuscular or subcutaneous) adj (immunoglobulin$ or antibod$ or gammaglobulin$)).mp.
10 exp IMMUNOGLOBULINS/
11 or/8-10
12 7 and 11
13 randomized controlled trial.pt.
14 controlled clinical trial.pt.
15 randomized controlled trials.sh.
16 random allocation.sh.
17 double blind method.sh.
18 single-blind method.sh.
19 or/13-18
20 (animals not human).sh.
21 19 not 20
22 clinical trial.pt.
23 exp clinical trials/
24 (clin$ adj25 trial$).ti,ab.
25 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
26 placebos.sh.
27 placebo$.ti,ab.
28 random$.ti,ab.

29 research design.sh.
30 or/22-29
31 30 not 20
32 31 not 21
33 comparative study.sh.
34 exp evaluation studies/
35 follow up studies.sh.
36 prospective studies.sh.
37 (control$ or prospectiv$ or volunteer$).ti,ab.
38 or/33-37
39 38 not 20
40 39 not (21 or 32)
41 21 or 32 or 40
42 12 and 41

Database : EMBASE (Ovid) 1980 – 2005 week 18
Search strategy (RCTs search)

1 ((immunoglobulin or antibody or gammaglobulin) adj (deficienc$ or defect$)).mp.
2 hypogammaglobulin?emia.mp. or exp HYPOGAMMAGLOBULINEMIA/
3 exp AGAMMAGLOBULINEMIA/ or agammaglobulin?emia.mp.
4 primary immunodeficienc$.tw.
5 CLL.mp.
6 chronic lymphocytic leuk?emia.mp. or exp Chronic Lymphatic Leukemia/
7 immunoglobulin deficienc$.tw.
8 or/1-7
9 ((immunoglobulin or antibody or gammaglobulin) adj (infusion$ or replacement$)).mp.
10 ((intravenous or intramuscular or subcutaneous) adj (immunoglobulin$ or antibod$ or gammaglobulin$)).mp.
11 exp IMMUNOGLOBULIN/
12 or/9-11
13 8 and 12
14 randomized controlled trial/
15 exp clinical trial/
16 exp controlled study/
17 double blind procedure/
18 randomization/
19 placebo/
20 single blind procedure/
21 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp.
22 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp.
23 (placebo$ or matched communities or matched schools or matched populations).mp.
24 (comparison group$ or control group$).mp.
25 (clinical trial$ or random$).mp.

26 (quasiexperimental or quasi experimental or pseudo experimental).mp.
27 matched pairs.mp.
28 or/14-27
29 13 and 28
30 limit 29 to human

Database: CINAHL - Cumulative Index to Nursing & Allied Health Literature 1982 to April week 4 2005
Search Strategy

1 ((immunoglobulin or antibody or gammaglobulin) adj (deficienc$ or defect$)).mp.
2 hypogammaglobulin?emia.mp. or exp Agammaglobulinemia/
3 primary immunodeficienc$.tw.
4 chronic lymphocytic leuk?emia.mp. or exp Leukemia, Lymphocytic, Chronic/
5 CLL.mp.
6 or/1-5
7 ((intravenous or intramuscular or subcutaneous) adj (immunoglobulin$ or antibod$ or gammaglobulin$)).mp.
8 ((immunoglobulin or antibody or gammagobulin) adj (infusion$ or replacement$)).mp.
9 or/7-8
10 6 and 9

Appendix 2

Data extract form (blank)

a. Data Extraction Form for RCT parallel trials

1. Parallel trials - Patient baseline characteristics Ref:

Category: First author and year of publication Condition Trial type	
Number of patients randomized	
Age (years) [Mean (SD)/Range]	
Sex [proportion male (%)]	
Condition	
Duration of condition	
Infection history	
Previous Ig treatment	
Serum IgG levels (g/L)	
Inclusion/exclusion criteria	
Comments	

2. Parallel trials - Treatment Ref:

Treatment	**Intervention**	**Comparator**
Type		
Route		
Dose/Frequency		
Rate or volume of infusion		
Setting		
Time length per treatment		
Treatment duration		
Interval between treatment episodes		
Concomitant treatment		
Follow up length		
Comments		

3. Parallel trials - Trial quality **Ref:**

Whether randomised / Randomisation method	
Whether blinded / Who	
Description of withdrawals (%) (Yes/ No)	
Jadad score	
Reason of withdrawal given (Yes/ No)	
Method of allocation concealment stated	
Analysis by intention to treat (Yes/No)	
Comments	

4. Parallel trials - Results -Total infections Ref:

Infections [a]	**Intervention**	**Comparator**	**Time point** (m)
Treatment			
Total N. of infection events / patients [b]			
N. of mild / moderate / severe infections or patients [b]			
Total N. of infection events per patient			
N. of patients infection free during the trial			
Duration of infection			

a. Including acute or exacerbation of chronic infections that were related to immunodeficiency; please enter Mean (SD)/Median/Range in the column if applicable.
b. If there is only one of the two options applicable, please highlight the one applicable.

5. Parallel trials - Results - Infection type Ref:

Infections [a]	**Intervention**	**Comparator**	**Time point** (m)
Treatment			
Type of infection			
N. of infection events			
N. of mild / moderate / severe infections			
N. of infection events per patient			
N. of patients infection free during the trial			
Duration of infection			
Duration of infection-free intervals			

a. Including acute or exacerbation of chronic infections that were immunodeficiency related; please enter Mean (SD) / Median / Range in the column if applicable.
b. Please specify the time point, otherwise it refers to the whole study period.

6. Parallel trials - Results -----Type and site of infections Ref:

Type and site [a]	Intervention arm [b] N. events / N. patients	Comparator arm [b] N. events / N. patients	Time point [c]

a. Please specify the infection types and sites;
b. If there is only one of the two options applicable, please highlight the one applicable;
c. Please specify the time point, otherwise it refers to the whole study period.

7. Parallel trials - other outcomes Ref:

Other outcomes	Intervention	Comparator	Time point
Total N. events of fever			
N. Events of fever per patient			
N. Patients had fever			
Days with fever			
N. Patients / days using antibiotics			
N. Patients using therapeutic antibiotics			
N. Patients using prophylactic antibiotics			
N. Antibiotic courses			
N. Antibiotic courses per patient			
N. Hospital admission			
N. Patients admitted to hospital			
Days in hospital			
N. Periods off work or school per patient			
N. Patient / days off work or school.			
Serum IgG levels (g/L)			
Mortality			
Quality of life			
Others			

8. Parallel trials - Results -- Adverse events Ref:

Adverse events [a]	Intervention	Comparator
Treatment		
N. Infusions		
N. Adverse event associated infusion		
N. Adverse events		
N. Patients with adverse event (s)		
N. Local reactions/ N. Patients with local reactions		
1. Swelling		
2. Soreness		
3. Redness		
4. Induration		
5. Local heat		
6. Itching		
7. Bruising		
8. Rash		
9. Others [b]		
N. Systemic reaction / N. Patients with systemic reactions		
1. Fever		
2. Headache		
3. Backache		
4. Perspiration		
5. Malaise		
6. Chills		
7. Nausea		
8. Tachycardia		
9. Dyspnea		
10. Others [b]		
N. Anaphylactoid / N. Patients with anaphylactoid		
Viral safety		
1. N. patients acquired hepatitis B		
2. N. patients acquired hepatitis C		
3. Others [b]		
Others		

a. Please indicate mild, moderate, and severe. If there is only one of the two options applicable, please highlight the one applicable.
b. Place specify the adverse events if applicable.

9. How were the outcomes measured?

b. Data Extraction Form for crossover I trials

1. Crossover trial - Patients baseline characteristics Ref:

Category **First author and year of publication;** **Condition;** **Trial type**	
Number of patients	
Age (years)[Mean (SD)/Range]	
Sex [proportion male (%)]	
Condition	
Duration of condition Mean (SD)/ Range	
Infection history Occasional/Recurrent/Major	
Previous Ig treatment Type, route, dose/frequency, duration	
Serum IgG levels (g/L)	
Inclusion/exclusion criteria	
Comments	

2. Crossover trial -Treatment Ref:

	Intervention	**Comparator**
Treatment type		
Treatment route		
Treatment dose/Frequency		
Rate or volume of infusion		
Setting		
Time length per treatment		
Interval between treatment Episodes		
Concomitant treatment		
Comments		

3. Crossover trial -Trial quality for RCTs **Ref:**

Whether randomised / Randomisation method	
Whether blinded / Who	
Description of withdrawals (%) (Yes/No)	
Jadad score	
Reason of withdrawal given (Yes/ No)	
Method of allocation concealment stated	
Analysis by intention to treat (Yes/No)	
Order effect analysis (Yes /No) and the results	
Comments	

4. Representation of Crossover Trial Ref:

Period 1	Intervention	Comparator
Treatment		
Number randomised		
Treatment duration		
Follow up length		
Number & time point & reason of withdrawal		
Number completed		

Washout duration =

Crossover of treatment

Period 2	Intervention	Comparator
Treatment		
Number of entry		
Treatment duration		
Follow up length		
Number & time point & reason of withdrawal		
Number completed		

Comments:

5. Crossover trial - Results - Total infections Ref:

Infections [a]	**Intervention**	**Comparator**	**Time point (m)** [b]
Treatment			
Total N. of infection events			
N. of mild / moderate / severe infections			
Total N. of infection events per patient			
N. of patient infection free during the trial			
Duration of infection			
Duration of infection-free intervals			

a. Including those of acute or exacerbation of chronic; please enter Mean (SD)/ Median/ Range in the column if applicable.

b. Please specify the trial period if applicable, otherwise it refers to the whole duration of the two periods.

6. Crossover trial - Results - Infection type Ref:

Infections [a]	**Intervention**	**Comparator**	**Time point (m)** [b]
Treatment			
Type of infection [c]			
N. Infection events			
N. Mild / Moderate / Severe infections			
N. Infection events per patient			
N. Patients infection free during the trial			
Duration of infection			
Duration of infection-free intervals			

a. Including acute or exacerbation of chronic infections that were immunodeficiency related; please enter Mean (SD)/ Median/ Range in the column if applicable.
b. Please specify the trial period if applicable; otherwise it refers to the whole duration of the two periods.
c. Please specify the infection type (e.g. sites defined, etc.)

7. Crossover trial - Type and site of infections Ref:

Type and site [a]	Intervention arm [b] (N. events / N. patients)	Comparator arm [b] (N. events / N. patients)	Trial period [c]
Treatment			

a. Please specify type or site of the infections;
b. If there is only one of the two options applicable, please highlight the one applicable;
c. Please specify the trial period (1 or 2), otherwise it refers to the whole study period.

8. Crossover trial - Results - Other outcomes Ref:

Other outcomes [a]	Intervention [b]	Comparator [b]	Time point
Treatment			
N. Events of fever			
N. Patients had fever			
N. Events of fever per patient			
Days with fever			
N. Patients / days using antibiotics [c]			
N. Patients / days using therapeutic antibiotics [c]			
N. Patients / days using prophylactic antibiotics [c]			
N. Antibiotic courses			
N. Antibiotic courses per patients			
N. Events of hospital admission			
N. Patients admitted to hospital			
Days in hospital			
N. Periods absent from work or school per patient			
N. Patients / days absent from work or school [c]			
Serum IgG levels (g/L)			
Mortality			
Quality of life [d]			
Others [e]			

a. Please enter Mean (SD) / Median / Range in the column if applicable.
b.Please specify the trial period if applicable.
c.If there is only one of the two options applicable, please highlight the one applicable.
d.Place enter scoring system used, eg. Euro QoL.
e.Place specify the type of the outcomes if applicable.

9. Crossover trial - Results - Adverse events Ref:

Adverse events [a]	**Intervention** [b]	**Comparator** [b]
Treatment		
N. Total infusions		
N. Adverse event associated infusions		
N. Adverse events		
N. Patients with adverse events		
N. Local reactions / N. Patients with local reactions [c]		
1. Swelling		
2. Soreness		
3. Redness		
4. Induration		
5. Local heat		
6. Itching		
7. Bruising		
8. Rash		
9. Others [d]		
N. Systemic reaction / **N. Patients with systemic reactions** [c]		
1. Fever		
2. Headache		
3. Backache		
4. Perspiration		
5. Malaise		
6. Chills		
7. Nausea		
8. Tachycardia		
9. Dyspnea		
10. Others [d]		
N. Anaphylactoid / N. patients with anaphylactoid [c]		
Viral safety		
1. N. patients acquired hepatitis B		
2. N. patients acquired hepatitis C		
3. Others [d]		
Others [d]		

a. Including mild, moderate, and severe.
b. Place enter trial period if applicable, otherwise it refers to the whole duration of the two periods.
c. If there is only one of the two options applicable please highlight the one applicable.
d. Place specify the adverse events if applicable.

10. Crossover trial ---- Results ---- patient preference Ref:

Preference	**Intervention**	**Comparator**
Treatment		
Total N. of patient completed the trial		
N. of patient preferred the treatment		
N. of patient without preference		

11. How were the outcomes measured?

Appendix 3

Cost effectiveness
Search strategies

Database: Cochrane Library (Wiley) Internet version 2005 Issue 2
Search strategy

#1 primary next immunodeficienc*
#2 secondary next immunodeficienc*
#3 immunologic next deficienc*
#4 impaired next immune
#5 immune next deficienc*
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 Ig next replacement
#8 immunoglobulin next replacement
#9 intravenous next immunoglobulin*
#10 intramuscular next immunoglobulin*
#11 subcutaneous next immunoglobulin*
#12 gammaglobulin next infusion*
#13 immunoglobulin next infusion*
#14 exp Immunoglobulins/
#15 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)
#16 (#6 AND #15)

Database: MEDLINE (Ovid) 1966 to July Week 1 2005
Search Strategy Cost search 1 :

1 primary immunodeficienc$.tw.
2 secondary immunodeficienc$.tw.
3 (immunologic adj2 deficienc$).tw.
4 (impaired adj immune).mp.
5 (immune adj deficienc$).mp.
6 exp Immunologic Deficiency Syndromes/
7 or/1-6
8 (Ig adj replacement).mp.
9 (immunoglobulin adj replacement).mp.
10 intravenous immunoglobulin$.mp. or exp Immunoglobulins, Intravenous/
11 intramuscular immunoglobulin$.mp.
12 subcutaneous immunoglobulin$.mp.
13 (gammaglobulin adj infusion$).mp.
14 (immunoglobulin adj infusion$).mp.
15 exp Immunoglobulins/
16 or/8-15
17 7 and 16
18 economics/
19 exp "costs and cost analysis"/

20 cost of illness/
21 exp health care costs/
22 economic value of life/
23 exp economics medical/
24 exp economics hospital/
25 economics pharmaceutical/
26 exp "fees and charges"/
27 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.
28 (expenditure$ not energy).tw.
29 (value adj1 money).tw.
30 budget$.tw.
31 or/18-30
32 17 and 31

Database: MEDLINE (Ovid) 1966 to July Week 1 2005
Search Strategy: Cost search 2

1 primary immunodeficienc$.tw.
2 secondary immunodeficienc$.tw.
3 (immunologic adj2 deficienc$).tw.
4 (impaired adj immune).mp.
5 (immune adj deficienc$).mp.
6 exp Immunologic Deficiency Syndromes/
7 or/1-6
8 (Ig adj replacement).mp.
9 (immunoglobulin adj replacement).mp.
10 intravenous immunoglobulin$.mp. or exp Immunoglobulins, Intravenous/
11 intramuscular immunoglobulin$.mp.
12 subcutaneous immunoglobulin$.mp.
13 (gammaglobulin adj infusion$).mp.
14 (immunoglobulin adj infusion$).mp.
15 exp Immunoglobulins/
16 or/8-15
17 7 and 16
18 economics/
19 exp "costs and cost analysis"/
20 cost of illness/
21 exp health care costs/
22 economic value of life/
23 exp economics medical/
24 exp economics hospital/
25 economics pharmaceutical/
26 exp "fees and charges"/
27 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.
28 (expenditure$ not energy).tw.
29 (value adj1 money).tw.

30 budget$.tw.
31 or/18-30
32 17 and 31
33 exp HIV/
34 human immuno$.tw.
35 or/33-34
36 32 and 35
37 32 not 36
38 32 not 35
39 from 38 keep 1-62

Database: MEDLINE (Ovid) 1966 to July Week 1 2005
Search Strategy QOL :

1 primary immunodeficienc$.tw.
2 secondary immunodeficienc$.tw.
3 (immunologic adj2 deficienc$).tw.
4 (impaired adj immune).mp.
5 (immune adj deficienc$).mp.
6 exp Immunologic Deficiency Syndromes/
7 or/1-6
8 (Ig adj replacement).mp.
9 (immunoglobulin adj replacement).mp.
10 intravenous immunoglobulin$.mp. or exp Immunoglobulins, Intravenous/
11 intramuscular immunoglobulin$.mp.
12 subcutaneous immunoglobulin$.mp.
13 (gammaglobulin adj infusion$).mp.
14 (immunoglobulin adj infusion$).mp.
15 exp Immunoglobulins/
16 or/8-15
17 7 and 16
18 quality of life/
19 life style/
20 health status/
21 health status indicators/
22 or/18-21
23 17 and 22
24 from 23 keep 1-14

Database: OHE HEED
2005 July issue

Search terms used:

antibod* or cvid or CLL or immunological or immunodeficienc* or myeloma or lymphocytic AND immunoglobulin*

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