Pharmacovigilance

Investigator Meeting

12th September 2017 – Sheffield

UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit | Hull and East Yorkshire Hospitals NHS Trust | NHS

Definitions – Adverse Event

- Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment

<u>In STOP-ACEi</u>

- Reported for duration of patient trial participation
- Reported on CRF for next trial visit

Definitions – Serious

- Any adverse event or reaction that:
  - Results in death
  - Is life-threatening
  - Requires hospitalisation or prolongs existing hospitalisation
  - Results in persistent or significant disability or incapacity
  - Consists of a congenital anomaly or birth defect

<u>In STOP-ACEi</u>

- Standard definitions used.
- Reported on an SAE form by fax.

Definitions – Adverse Reaction

- Any untoward response in a participant to an investigational medicinal product which is related to any dose administered to that participant.
- Relatedness must be determined by medically qualified personnel.

<u>In STOP-ACEi</u>

- The IMPs are:
  - Any ACEi/ARB used in control arm
- Also consider:
  - ACEi/ARB discontinuation in experimental arm

Definitions – Adverse Reaction

Trial intervention causality assessment. The assessment of causality must be provided by a clinician.

For the control arm (continue ACEi/ARB), is the SAE related to the particular ACEi and/or ARB the participant is taking?

For the experimental arm (discontinue ACEi/ARB), is the SAE related to the withdrawal of ACEi/ARB treatment?

Date of randomisation:	Date last dose of ACEi/ARB taken:	Causality Assessment: 1 Unrelated to trial intervention 2 Unlikely to be related to trial intervention 3 Possibly related to trial intervention 4 Probably related to trial intervention 5 Definitely related to trial intervention	Action taken due to SAE: 1 Treatment permanently discontinued (or if on discontinue arm, treatment re-commenced). 2 Dose reduced 3 Dose increased 4 Dose not changed 5 Unknown 6 N/A
DD / MMM / YYYY	DD / MMM / YYYY	☐	☐

Please give reasons why you consider the event to be related to ACEi/ARB treatment or withdrawal:

.....

.....

If treatment was altered, did the reaction abate after drug changes? No ☐ Yes ☐ N/A ☐

Definitions – Unexpected

- An adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product set out in the SmPC or IB for that product.

<u>In STOP-ACEi</u>

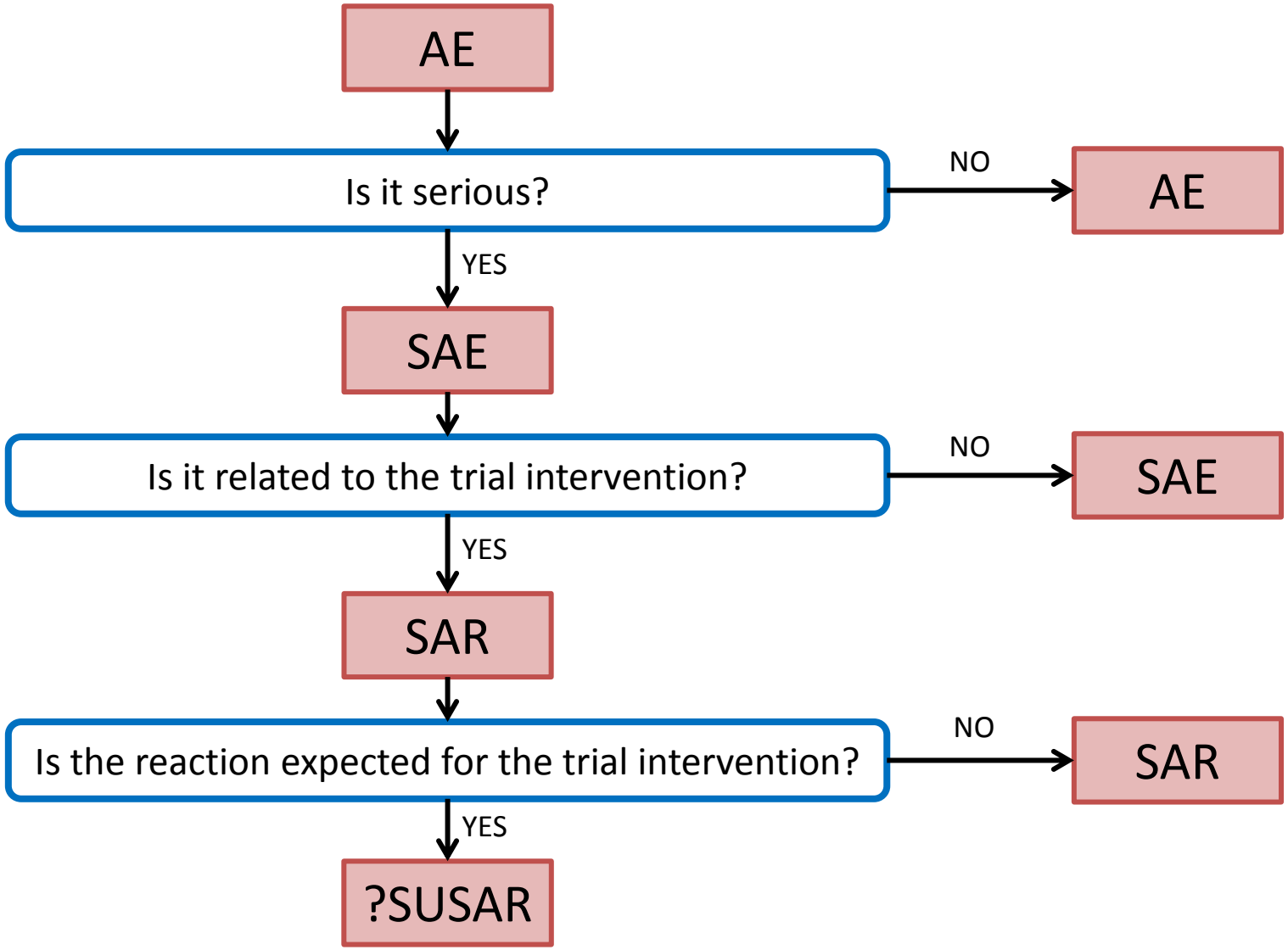
- Use SmPC for ACEi or ARB
- Use protocol for discontinuation of ACEi or ARB
  - Hypertension
  - Increased peripheral oedema
  - Gout
  - Change in proteinuria
  - Hypokalaemia
  - Weight gain
  - Increase in breathlessness
- Most events/reactions will be expected

Definitions – Unexpected

Was the SAE unexpected, i.e. of a type or severity which is NOT consistent with the up-to-date SmPC (available at http://emc.medicines.org.uk/) or events potentially related to ACEi/ARB withdrawal, as outlined in protocol section 10.1? This section must be completed by a clinician.

Unexpected ☐	Expected ☐	Unrelated ☐
If Unexpected, please give reasons why you consider the event to be unexpected:		
.....		

Definitions – Summary



Reporting – why?

Why are we reporting adverse events for STOP-ACEi?

- Secondary outcome:

  To test that withdrawal of these treatments does not cause excess harm (e.g. increased cardiovascular events such as heart failure, hypertension, myocardial infarction, stroke) and is not associated with an increase in adverse effects.

- To add to the safety profile of the drugs/intervention and comply with the regulations

Reporting – what?

What adverse events are we reporting for STOP-ACEi?

- All AEs should be reported on the visit CRF and in medical notes
  - Whether serious or not
  - Whether expected or not
- SAEs (including SUSARs) should also be reported on an SAE form and faxed to BCTU within 24 hours of being notified of the event
- SAEs that don't need to be reported on an SAE form
  - Hospitalisations for:
    - Routine treatment or monitoring of the studied indication that is not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened

Reporting – how?

CRFs

Non-serious

Serious

Fax – 0121 415 9135
Within 24 hrs of notification

CI

Sponsor

DMC

MREC

MHRA

Table of Causality

Category	Definition
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration or discontinuation of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events)
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration or discontinuation of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments)
Not related	There is no evidence of any causal relationship

Issues for STOP-ACEi - Causality

- Assessment of causality will determine if a serious event is an SAE or an SAR

- Is the event related to ACEi/ARB withdrawal or CKD?
  - Consider timeline
  - Protocol guidance: within 3 months of withdrawal is more likely to be a reaction to withdrawal
- Existing evidence suggests no difference in CV events when using ACEi/ARB therapy vs. non-ACEi/ARB therapy to control BP
- DMEC will be best placed to determine if there is a causal relationship – whole population data vs. single event reporting

Issues for STOP-ACEi - Expectedness

- Assessment of expectedness will determine if a serious and related event is an SAR or a SUSAR

- What do we expect when withdrawing ACEi/ARB?
  - Increased CV events?
  - Hypertension?
- Disease progression may confound assessment
- Blood pressure should remain controlled with other antihypertensives

Oversight

- The Data Monitoring and Ethics Committee
  - Trial Statistician
  - Consultant Cardiologist
  - Consultant Nephrologist
- Purpose
  - To safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, ensure the trial collects the necessary information to address the trial question and monitor the overall conduct of the clinical trial.
- Data reviewed:
  - Patient safety
  - Treatment efficacy
  - AEs/SAEs
  - Data return rates
  - Recruitment
  - Data quality