SITE REFRESHER TRAINING TRIAL MANAGEMENT

STAMPEDE

Systemic **T**herapy in **A**dvancing or **M**etastatic **P**rostate Cancer: **E**valuation of **D**rug **E**fficacy

May 2020

Version 1.0

What we will be covering…..

- Pharmacovigilance
- Covid-19

PHARMACOVIGILANCE

What is Pharmacovigilance?

- The World Health Organization (WHO) defines pharmacovigilance (PV) as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.”
- PV ensures that a patient’s safety and wellbeing is safeguarded throughout the entire drug development lifecycle, including when the drug is readily available on the market.
- Pharmacovigilance is crucial during the clinical research phase of drug development as to determine whether a potential new drug is safe and effective. It is the practice of pharmacovigilance that enables researchers and drug developers to rigorously assess the safety of the new drug.

Event Definitions

Adverse Event (AE)

- Any untoward medical occurrence in a patient or clinical trial patient to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Serious Adverse Event (SAE)

- Any AE that: o results in death, o is life-threatening o requires inpatient hospitalization or causes prolongation of existing hospitalization o results in persistent or significant disability/incapacity, o is a congenital anomaly/birth defect, or o requires intervention to prevent permanent impairment or damage

Adverse Reaction (AR)

- Any AE that is deemed to have a causal relationship to the research treatment.

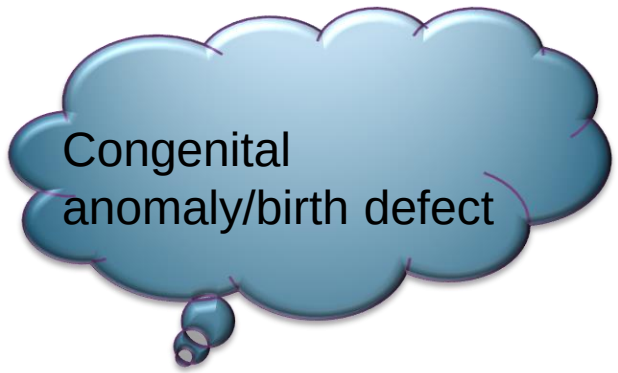
Serious Adverse Reaction (SAR)

- Any SAE that is deemed to have a causal relationship to the research treatment. Or
- Any AR that meets the definition of serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

- Any SAR that is not an expected side effect of the research treatment.

Reporting Criteria



Reporting Exemptions

If the patients event falls into any of the following exemption groups, they do not fulfil the STAMPEDE definition of an SAE and only need reporting on a follow up toxicity form

Serious adverse events unrelated to protocol treatment i.e. unrelated SAEs (refer to Section 11.1.2) occurring more than 30 days after stopping protocol treatment.

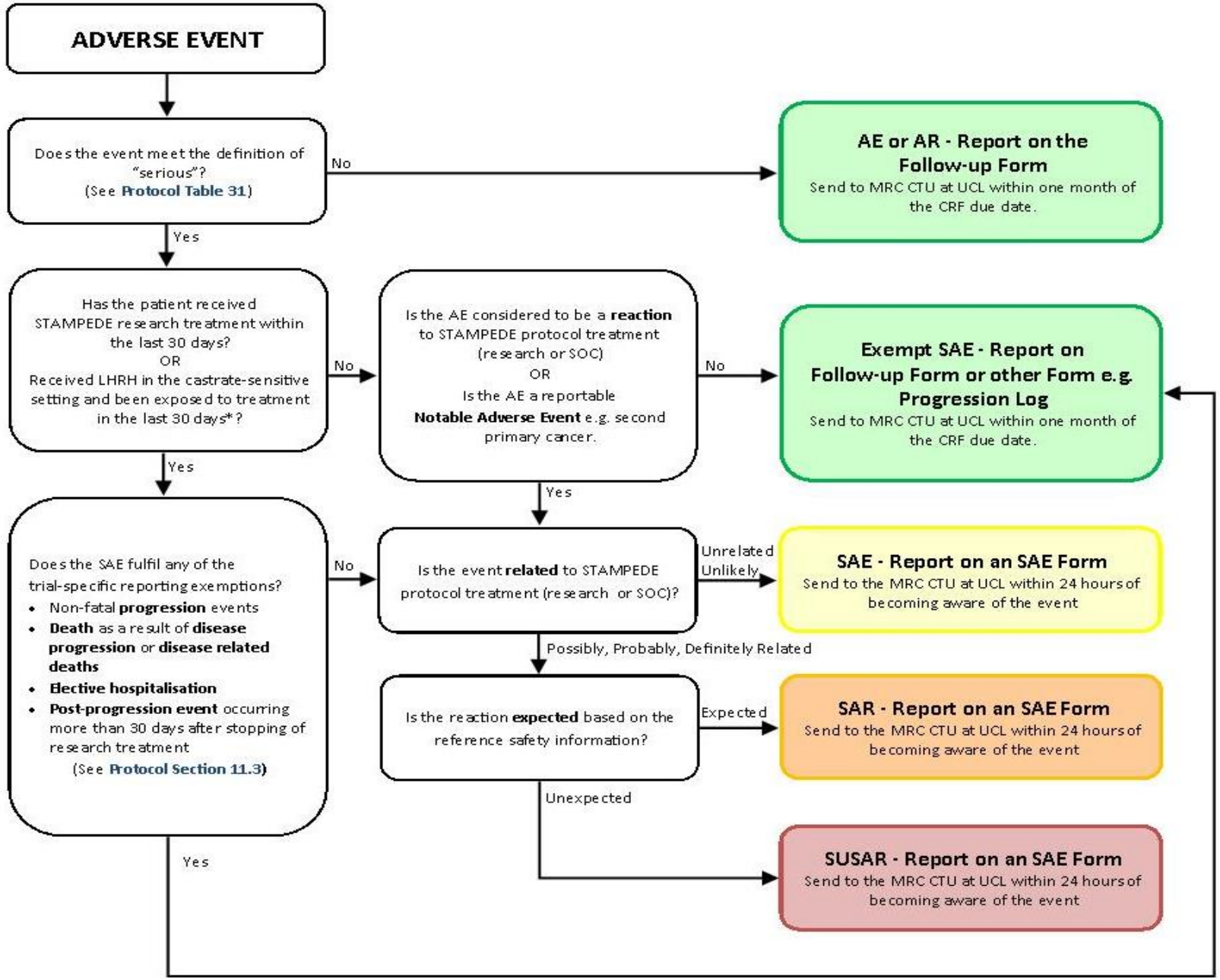
Serious adverse events occurring after disease progression that are unrelated (i.e. not SARs or SUSARs) to protocol treatment are exempt, providing protocol treatment stopped at least 30 days ago.
N.B non-protocol treatment includes ADT in CRPC setting, therefore the 30 day rule does not apply for patients continuing on ADT alone. (Refer to Section 11.1.2)

Non-fatal progression events: events that fulfil the definition of serious e.g. result in hospital admission, but are due to disease progression are exempt from reporting as an SAE, instead details should be provided on the Progression Log.

Death as a result of disease progression or disease-related deaths: Do not complete an SAE CRF, instead details should be reported on the Death Form.

Elective hospitalisation and surgery for treatment of locally-advanced or metastatic prostate cancer or its complications. These should be recorded as a non-trial inpatient admission on the follow-up form under Non-Trial visits.

Elective hospitalisation to simplify treatment or procedures. If related to prostate cancer, record as non-trial inpatient admission on the follow-up form. If unrelated e.g. pre-existing conditions that have not been exacerbated by protocol treatment, do not report.


ADVERSE EVENT
Does the event meet the definition of "serious"? (See Protocol Table 31)
No
AE or AR - Report on the Follow-up Form
Send to MRC CTU at UCL within one month of the CRF due date.
Yes
Has the patient received STAMPEDE research treatment within the last 30 days? OR Received LHRH in the castrate-sensitive setting and been exposed to treatment in the last 30 days*?
No
Is the AE considered to be a reaction to STAMPEDE protocol treatment (research or SOC) OR Is the AE a reportable Notable Adverse Event e.g. second primary cancer.
No
Exempt SAE - Report on Follow-up Form or other Form e.g. Progression Log
Send to MRC CTU at UCL within one month of the CRF due date.
Yes
Yes
Does the SAE fulfil any of the trial-specific reporting exemptions?
• Non-fatal progression events
• Death as a result of disease progression or disease related deaths
• Elective hospitalisation
• Post-progression event occurring more than 30 days after stopping of research treatment
(See Protocol Section 11.3)
No
Is the event related to STAMPEDE protocol treatment (research or SOC)?
Unrelated Unlikely
SAE - Report on an SAE Form
Send to the MRC CTU at UCL within 24 hours of becoming aware of the event
Possibly, Probably, Definitely Related
Is the reaction expected based on the reference safety information?
Expected
SAR - Report on an SAE Form
Send to the MRC CTU at UCL within 24 hours of becoming aware of the event
Unexpected
SUSAR - Report on an SAE Form
Send to the MRC CTU at UCL within 24 hours of becoming aware of the event
Yes

Common problems seen

- **Missing trial treatment details**
  - A. HT, Abiraterone, Enzalutamide and Docetaxel
  - B. Abiraterone, Enzalutamide
  - C. HT, Abiraterone and Enzalutamide

    - A. HT and Docetaxel
    - B. HT and RT
    - C. HT alone

Patient allocated to Arm J and at baseline data provided stated patient would be receiving Docetaxel as part of SOC

Patient allocated to Arm H, the patient refused his RT treatment and continued along with just HT. No Docetaxel was reported at baseline

- **Inclusion of second line treatments (we don't need this)**
- **Causality – this is a clinical judgement based on information available.**
- **Expectedness – this is based on what is in the SPC or IB, not clinical experience**
- **Not enough information to support the event term or CTCAE grade**
  - falls can be caused by lots of things – be specific
  - not everything is grade 3 because patient was hospitalised
- **No staff signature (report is not valid without this)**

RSI

Drug Name	Approved RSI for SAE expectedness assessment									
Zoledronic Acid (Zometa)	**05-Oct-05 to 07-Oct-18**			**07-Oct-18 to 16-Oct-19**			**17-Oct-19 onwards**			
	Section 4.8 of Zometa 4mg/5ml SmPC 22-Mar-05 (updated on EMC 11 Apr 2005)			Section 4.8 of Zometa 4mg/5ml SmPC13-Jul-18 (updated on EMC 23-Jul-2018)			Section 4.8 of Zometa 4mg/5ml SmPC 15-Jun-17 (updated on EMC 05-Jul-2017)			
Docetaxel (Taxotere)	**05-Oct-05 to 23-Nov-15**			**24-Nov-15 to 15-May-19**			**16-May-19 to 16 Oct-19**			**17-Oct-19 onwards**
	Section 4.8 of Docetaxel (Taxotere) 20mg and 80mg per 4 ml SmPC 24-Jan-05 (updated EMC 20-May-2005)			Section 4.8 of Docetaxel (Taxotere) 80mg/4ml SmPC 21-May-15 (updated on EMC 01-Jun-2015)			Section 4.8 of Docetaxel (Taxotere) 80mg per 4 ml SmPC 12-May-16 (updated on EMC 04-Nov-2016)			Section 4.8 of Docetaxel (Seacross) 20mg per 1 ml SmPC 14-Mar-18 (updated on EMC 28-Sept-2018)
Celecoxib (Celebrex)	**05-Oct-05 to 16-Oct-18**			**17-Oct-18 to 16-Oct-19**			**17-Oct-19 onwards**			
	Section 4.8 of Celebrex 200mg SmPC Mar-03 (updated on EMC 29-May-2003)			Section 4.8 of Celebrex 200mg SmPC Sept-17 (updated on EMC 30-Jan-2018)			Section 4.8 of Celebrex 200mg SmPC 01-Oct-18 (updated on EMC 21-May-2019)			
Abiraterone (Zytiga)	**03-Oct-11 to 28-Nov-12**	**29-Nov12 to 16-Apr-14**	**17-Apr-14 to 18-Mar-15**	**19-Mar-15 to 23-Nov-15**	**24-Nov-15 to 22-Nov-17**	**23-Nov-17 to 11-Oct-18**	**12-Oct-18 to 15-May-19**	**16-May-19 to 16-Oct-19**	**17-Oct-19 onwards**	
	IB Edition 8 (04-Apr-2011)	IB Edition 9 (27-Apr-2012) + Erratum	IB Edition 10 (26-Aug-2013)	IB Edition 11 (22-Sept-2014) + Addendum 1 (10-Dec-2014)	IB Edition 12 (26-Aug-2015)	IB Edition 13 (27-July-2017)	IB Edition 13 (27-July-2017) + Addendum 2 (20-Jun-2018)	IB Edition 13 (27-July-2017) + Addendum 3 (04-Sept-2018)	Section 4.8 of Abiraterone SmPC 26-Feb-19 (updated on EMC 04-Mar-2019)	
Enzalutamide (Xtandi)	**17-JApr-14 to 18-Mar-15**	**19-Mar-15 to 23-Nov-15**	**24-Nov-15 to 24-Apr-16**	**25-Apr-16 to 08-May-18**	**09-May-2018 to 11-Oct-18**	**12-Oct-18 to 16-Oct-19**	**17-Oct-19 onwards**			
	IB – Edition 6 (31-Jan-2013)	IB – Edition 7 (29-Apr-2014)	IB – Edition 8 (09-June-2015)	IB Edition 8 (09-June-2015) + Addendum 1 (17-Dec-2015)	IB – Edition 9 (01-June-2016)	IB - Edition 10 (18-June-2018)	Table 17 in IB - Edition 11 (10-Jun-2019)			

RSI

Metformin (Glucophage)	**24-Apr-16 to 15-May-19**	**16-May-19 to 16-Oct-19**	**17-Oct-19 onwards**
	Section 4.8 of Glucophage SmPC 500mg and 850mg Jan-15 (updated on EMC 23-Jan-15)	Section 4.8 of Glucophage SmPC 850mg Dec-16 (19-Jan-2017)	Section 4.8 of Glucophage SmPC 850mg Aug-2019 (updated on EMC 10-Sept-2019)
Transdermal Oestradiol (Progynova)	**14-Mar-17 to 15-May-19**	**16-May-19 onwards**	
	Section 4.8 of Progynova SmPC 12-Jan-2017 (updated on EMC 30-Jan-2017)	Section 4.8 of Progynova SmPC 31-Aug-17 (updated on EMC 29-Sept-2017)	
Leuprorelin (Prostap)	**14-Mar-17 to 15-May-19**	**16-May-19 to 16-Oct-19**	**17-Oct-19 onwards**
	Sections 4.4, 4.5 and 4.8 of leuprorelin 11.25mg SmPC 16-Mar-16 (updated on EMC 05-Apr-2016)	Sections 4.4, 4.5 and 4.8 of leuprorelin 11.25mg SmPC 11-Sep-18 (updated on EMC 05-Oct-2018)	Sections 4.4, 4.5 and 4.8 of **goserelin*** 10.8mg SmPC 24-Jan-17 (updated on EMC 07-Feb-2017)
Goserelin (Zoladex)	**14-Mar-17 onwards**		
	Sections 4.4, 4.5 and 4.8 of goserelin 10.8mg SmPC 24-Jan-17 (updated on EMC 07-Feb-2017)		
Triptorelin (Decapeptyl)	**14-Mar-17 to 16-Oct-19**	**17-Oct-19 onwards**	
	Sections 4.4, 4.5 and 4.8 of triptorelin 11.25mg SmPC 28-Apr-16 (updated on EMC 05-May-2016)	Sections 4.4, 4.5 and 4.8 of **goserelin*** 10.8mg SmPC 24-Jan-17 (updated on EMC 07-Feb-2017)	
Degaralix	**14-Mar-17 onwards**		
	Sections 4.4, 4.5 and 4.8 of degarelix acetate 80mg SmPC 21-Nov-14 (updated on EMC 21-Mar-2017)		

*RSI for leuprorelin and triptorelin 17-Oct-2019 onwards: the goserelin SPC sections 4.4, 4.5 and 4.8 will be used as RSI for all three LHRH agonists in STAMPEDE (goserelin, leuprorelin and triptorelin) due to these IMP belonging to the same ATC code (L02AE). This approach was submitted as a substantial amendment and approved by MHRA on 04-Nov-2019.

Event reporting

MHRA Guidance

- Capacity issues may result in delays in reporting. Timely reporting is important to protect the safety of participants.
- Expectedness assessments can be performed by the Sponsor, if these have previously been delegated to the site in order to reduce workload. This change would not need MHRA authorisation.

SAE SUBMISSION

HOW SHOULD SAEs BE SUBMITTED??

Email- mrcctu.stampede@ucl.ac.uk **OR** Fax- 020 7670 4818

- SAE forms sent via email should be sent securely with ‘SAE’ in the email subject title, using Galaxkey or another secure email provider which may be used locally.
- Please contact the team via email to get access to Galaxkey.

COVID-19 Update

COVID-19

Source of information

http://www.stampedetrial.org/centres/information-on-covid-19/

Randomisation

- 9th April- Pause to recruitment

Trial Treatment & Covid-19

- There is currently no evidence that any of the treatments used in STAMPEDE either increase the risk of infection with COVID-19 or are dangerous to continue if a patient has COVID-19 symptoms
  - But if a patient does become unwell with suspected COVID-19 infection, it is at the discretion of the treating clinician to decide whether to continue or with-hold any STAMEPEDE medication.

Follow-up Assessments

- Follow-up visits can be conducted via phone to reduce patient exposure wherever necessary.
  - The STAMPEDE Telephone Follow-Up Checklist is available on the website for guidance. http://www.stampedetrial.org/media/2401/stampede_telephone_consultation_checklist_v20.pdf
- Any missed assessments (e.g. blood tests, scans, BP) should be noted on the CRF to confirm the reason they have been missed and these will not be queried as missing data.
- It is acceptable for patients to self-measure blood pressure using home equipment.
- Quality of life sub study – patients can be sent blank forms for completion by post or e-mail.

IMP General Overview

- If patients are unable to perform safety blood tests, treatment should be discontinued until the necessary safety investigations are available.
- Patients pausing treatment due to being unable to complete safety testing, can restart treatment once testing continues. Provided the local clinician feels it remains in the patients best interests.
- Physicians can consider extending prescriptions to give a 4-month supply of Abiraterone and Enzalutamide.
- For Metformin, a 6 month prescription can be given to work alongside the blood testing for patients who have been on trial Metformin for 12 months and tolerated the treatment well.

Safety Testing

Abiraterone, Prednisolone and Enzalutamide

- Physicians can consider 3 monthly safety tests (K+, LFTs and BP)
  - The reduced testing must be in the patients benefit and the patient must be able to attend when they are thought necessary.
  - Patients are able to carry out at home blood pressure monitoring but must record the outcomes and share this with the research team
  - If safety testing cannot be carried out the patient's treatment should be discontinued until safety testing can be completed –although prednisolone treatment should continue

Metformin

- If a patient is unable to complete their 6 monthly safety tests (renal function) they should stop taking Metformin until they have had the opportunity for medical review.
  - For most patients, blood tests for cancer monitoring will remain essential and hence we do not anticipate this should be a problem.

Safety Testing

Transdermal Oestradiol

- If it becomes impossible to monitor patients' oestradiol and testosterone levels, it may on occasion be necessary to switch patients to LHRHa treatment to ensure androgen suppression is maintained.
- For patients with good disease control (e.g. low, stable PSA readings or oestradiol remaining below 2000), the safest course of action may be to continue the patches with regular monitoring being resumed as soon as possible, rather than switching to ADT.
- Clearly this risk benefit needs to be assessed on a patient by patient basis.

IMP Delivery

- **Abi or Abi+Enza**
  - ✓ Courier
  - ✓ Car collection, patient receive a text from pharmacy when their prescription is ready and a member of staff delivers to the car.
  - ✓ NHS staff taking IMP to the patient's home address - suitable precautions should be applied to avoid transmission.
- **All other treatments**
  - ✓ Royal Mail or other postage services
  - ✓ Courier
  - ✓ Car collection, patient receive a text from pharmacy when their prescription is ready and a member of staff delivers to the car.
  - ✓ NHS staff taking IMP to the patient's home address - suitable precautions should be applied to avoid transmission.
- Temperature monitoring is NOT required for these IMP

Deviation Overview

- The MHRA have given clear guidance about recording **deviations**, as there is a high probability of these occurring while research teams deal with the challenges of the COVID-19 pandemic.

- Please ensure all deviations that occur are recorded using the **Site deviation log.**

Deviations Log

Deviations tab

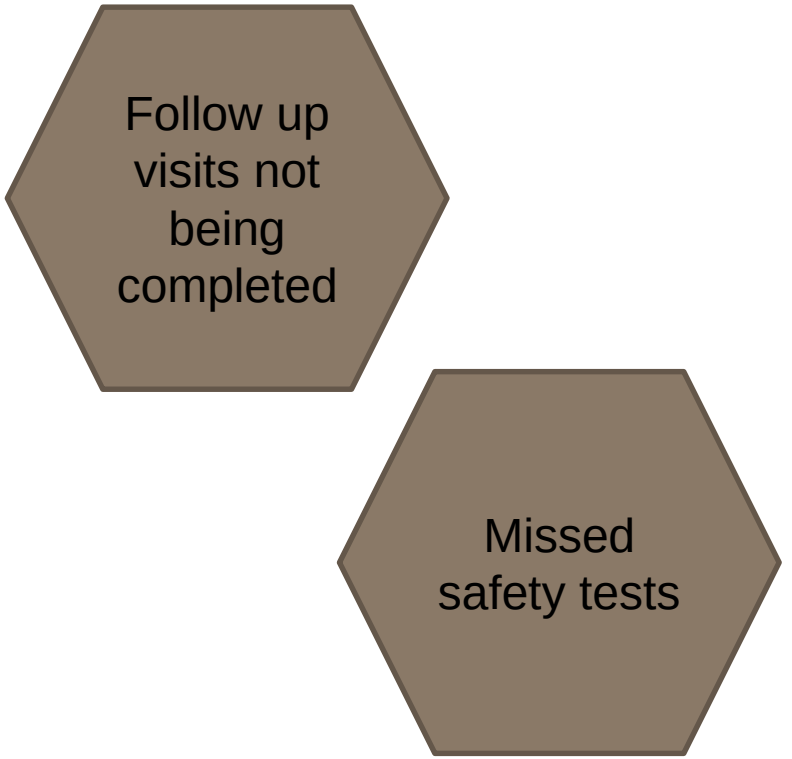
Trial	STAMPEDE											
Site												
Site No.												
Site Deviation No	Staff Membe Responsible	Deviation Summary	Date Site Beca Aware	Deviation Category?	Description If Othe	Patient(s) Affected I	Deviation Details	Date STAMPED Team Informe	Severit	Actions Required (CAPA, File No	Current Statu (Open or Clos
1	MB	Patient Missed Week 48 F/up									
2											
3											
4											
5											
6											

PI signoff tab

Trial	STAMPEDE	Site Deviations Log					
Site		Please print this table for the PI to review and sign once deviations have been closed. Ensure the height of each row is altered to include all information.					
Site No.							
Sites Deviation No.	Deviation Summary	Date site became awa	Patient(s) Affected	Severity	Current Status? (Open or Closed)	PI signature upon closure	Date PI signed
1	Patient Missed Week 48 F/up						
2							
3							
4							

Deviations

- **Critical Deviation** - Any change, divergence, or departure from study protocol **that significantly** impacts patients' rights, safety and/or well-being or significantly impacts the integrity and/or reliability of study results.
- **Major Deviation** - Any change, divergence, or departure from study protocol **that may** impact the patients' rights, safety and/or well-being or significantly impact the completeness, accuracy and/or reliability of study data
- **Other Deviation** - Any deviation that will not adversely affect patients'/data but should be dealt with appropriately.



Any questions?