PHARMACOVIGILANCE OVERVIEW

STAMPEDE

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

November 2018

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:
  - results in death,
  - is life-threatening
  - requires inpatient hospitalization or causes prolongation of existing hospitalization
  - results in persistent or significant disability/incapacity,
  - is a congenital anomaly/birth defect, or
  - 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.

STAMPEDE Events

Adverse events (AE) include:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition (event through it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or a symptom present at baseline that worsens following administration of the study treatment

Serious Adverse Events (SAE)

- Are AEs that fulfil the definition of serious as detailed in Table 31 of the STAMPEDE protocol.
- SAEs are reported using the SAE CRF.
- If the event is assessed as possibly, probably or definitely related to treatment, it is categorised as a Serious Adverse Reaction (SARs). If the reaction is unexpected based on the product reference safety information, it is categorised as a Suspected Unexpected Serious Adverse Reaction (SUSAR), see Table 32 within the protocol.

Notable Adverse Events (NAE);

- Any new primary cancers which should be reported as a NAE on a SAE CRF for expedited clinical review. Except non-melanoma skin cancer (e.g. basal cell carcinomas and squamous cell carcinomas) which should be recorded as an AE on the Toxicity (AE) CRF.
- Other NAEs include pregnancy occurring in a partner of a STAMPEDE participant. This must also be reported on an SAE CRF.
- Pregnancies must be followed up until outcome, whether this is a live birth, stillbirth, or planned or spontaneous abortion.

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.

Expectedness & Causality

Expectedness

- The expectedness of a research treatment to an event is either:
  - Expected
  - Unexpected

Expected Events

- Are listed in the Investigators Brochure (IB), the Summary of Product Characteristics (SPC)

Unexpected Events

- Are not listed in the IB, the SPC as a side effect or is a more severe reaction than listed within the IB or SPC.

Causality

- The causal relationship of a research treatment to an event is any of the following:
  - Definitely
  - Probably
  - Possibly
  - Unlikely
  - Not Related
  - Administration
- Causality is an objective assessment by the treating clinician.

Event Classification

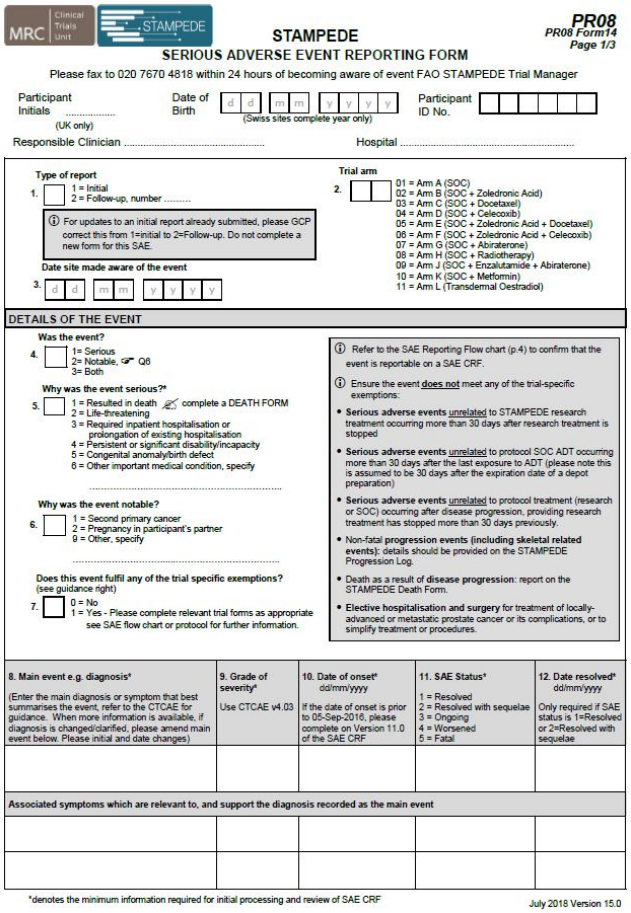
<table>
<tr><th rowspan="2">Causality</th><th colspan="2">Expectedness</th></tr>
<tr><th>1. Expected</th><th>2. Unexpected</th></tr>
<tr><td>1. Definitely
2. Probably
3. Possibly</td><td>SAR</td><td>SUSAR</td></tr>
<tr><td>4. Unlikely
5. Not Related
6. Administration</td><td colspan="2">SAE</td></tr>
</table>

STAMPEDE SAE Form CRF

Sites are required to submit any events within 24hrs of being made aware

Minimum data set
All questions marked with (*) is the minimum information required on initial submission of an event

Exemptions
Please ensure you refer to the exemptions guidance provided when completing question 7.
This information can also be located in section 11.2 of the protocol



MRC Clinical Trials Unit | STAMPEDE

STAMPEDE
SERIOUS ADVERSE EVENT REPORTING FORM

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PR08 Form14
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Please fax to 020 7670 4818 within 24 hours of becoming aware of event FAO STAMPEDE Trial Manager

Participant Initials ..... (UK only)
Date of Birth d d m m y y y y (Swiss sites complete year only)
Participant ID No.
Responsible Clinician .....
Hospital .....

Type of report
1. ☐ 1 = Initial
2 = Follow-up, number .....

ⓘ For updates to an initial report already submitted, please GCP correct this from 1=initial to 2=Follow-up. Do not complete a new form for this SAE.

Date site made aware of the event
3. d d m m y y y y

Trial arm
2. ☐☐
01 = Arm A (SOC)
02 = Arm B (SOC + Zoledronic Acid)
03 = Arm C (SOC + Docetaxel)
04 = Arm D (SOC + Celecoxib)
05 = Arm E (SOC + Zoledronic Acid + Docetaxel)
06 = Arm F (SOC + Zoledronic Acid + Celecoxib)
07 = Arm G (SOC + Abiraterone)
08 = Arm H (SOC + Radiotherapy)
09 = Arm J (SOC + Enzalutamide + Abiraterone)
10 = Arm K (SOC + Metformin)
11 = Arm L (Transdermal Oestradiol)

DETAILS OF THE EVENT

Was the event?
4. ☐ 1= Serious
2= Notable, ☞ Q6
3= Both

Why was the event serious?*
5. ☐ 1 = Resulted in death ✍ complete a DEATH FORM
2 = Life-threatening
3 = Required inpatient hospitalisation or prolongation of existing hospitalisation
4 = Persistent or significant disability/incapacity
5 = Congenital anomaly/birth defect
6 = Other important medical condition, specify
.....

Why was the event notable?
6. ☐ 1 = Second primary cancer
2 = Pregnancy in participant's partner
9 = Other, specify
.....

Does this event fulfil any of the trial specific exemptions? (see guidance right)
7. ☐ 0 = No
1 = Yes - Please complete relevant trial forms as appropriate see SAE flow chart or protocol for further information.

ⓘ Refer to the SAE Reporting Flow chart (p.4) to confirm that the event is reportable on a SAE CRF.

ⓘ Ensure the event **does not** meet any of the trial-specific exemptions:

- **Serious adverse events** unrelated to STAMPEDE research treatment occurring more than 30 days after research treatment is stopped
- **Serious adverse events** unrelated to protocol SOC ADT occurring more than 30 days after the last exposure to ADT (please note this is assumed to be 30 days after the expiration date of a depot preparation)
- **Serious adverse events** unrelated to protocol treatment (research or SOC) occurring after disease progression, providing research treatment has stopped more than 30 days previously.
- Non-fatal **progression events (including skeletal related events)**: details should be provided on the STAMPEDE Progression Log.
- Death as a result of **disease progression**: report on the STAMPEDE Death Form.
- **Elective hospitalisation and surgery** for treatment of locally-advanced or metastatic prostate cancer or its complications, or to simplify treatment or procedures.

8. Main event e.g. diagnosis* (Enter the main diagnosis or symptom that best summarises the event, refer to the CTCAE for guidance. When more information is available, if diagnosis is changed/clarified, please amend main event below. Please initial and date changes)	9. Grade of severity* Use CTCAE v4.03	10. Date of onset* dd/mm/yyyy If the date of onset is prior to 05-Sep-2016, please complete on Version 11.0 of the SAE CRF	11. SAE Status* 1 = Resolved 2 = Resolved with sequelae 3 = Ongoing 4 = Worsened 5 = Fatal	12. Date resolved* dd/mm/yyyy Only required if SAE status is 1=Resolved or 2=Resolved with sequelae
Associated symptoms which are relevant to, and support the diagnosis recorded as the main event				

*denotes the minimum information required for initial processing and review of SAE CRF

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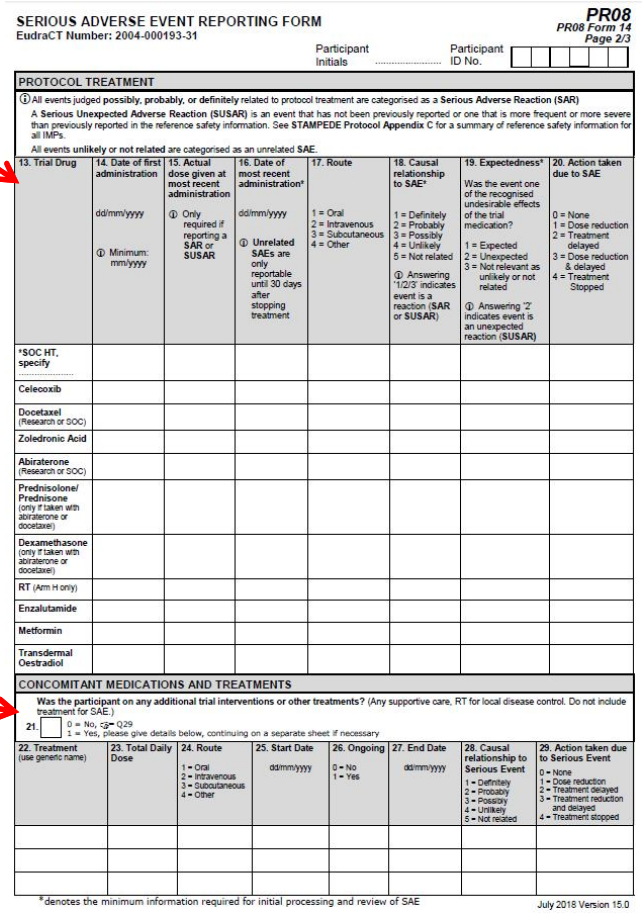
STAMPEDE SAE Form CRF

Medication detailed in this table should be related to the protocol research treatment and SOC (including Docetaxel), which the patient received for their allocated arm (e.g. Arm K-SOC & Metformin).

- Ensure Causal relationship and Expectedness are completed for all events & medications
- In some instances we may contact the site for confirmation on reviewers causal relation and expectedness, this will only be if internal reviewers feel it is expected as per the SPC or IB

Any additional treatment the patient receives following trial treatment or along side should be recorded in the concomitant medication table



SERIOUS ADVERSE EVENT REPORTING FORM
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Participant Initials ..... Participant ID No.

PROTOCOL TREATMENT

ⓘ All events judged **possibly, probably, or definitely** related to protocol treatment are categorised as a **Serious Adverse Reaction (SAR)**

A **Serious Unexpected Adverse Reaction (SUSAR)** is an event that has not been previously reported or one that is more frequent or more severe than previously reported in the reference safety information. See **STAMPEDE Protocol Appendix C** for a summary of reference safety information for all IMPs.

All events **unlikely or not related** are categorised as an unrelated **SAE**.

13. Trial Drug	14. Date of first administration dd/mm/yyyy ⓘ Minimum: mm/yyyy	15. Actual dose given at most recent administration ⓘ Only required if reporting a **SAR** or **SUSAR**	16. Date of most recent administration* dd/mm/yyyy ⓘ **Unrelated SAEs** are only reportable until 30 days after stopping treatment	17. Route 1 = Oral 2 = Intravenous 3 = Subcutaneous 4 = Other	18. Causal relationship to SAE* 1 = Definitely 2 = Probably 3 = Possibly 4 = Unlikely 5 = Not related ⓘ Answering '1/2/3' indicates event is a reaction (**SAR** or **SUSAR**)	19. Expectedness* Was the event one of the recognised undesirable effects of the trial medication? 1 = Expected 2 = Unexpected 3 = Not relevant as unlikely or not related ⓘ Answering '2' indicates event is an unexpected reaction (**SUSAR**)	20. Action taken due to SAE 0 = None 1 = Dose reduction 2 = Treatment delayed 3 = Dose reduction & delayed 4 = Treatment Stopped
*SOC HT, specify							
Celecoxib							
Docetaxel (Research or SOC)							
Zoledronic Acid							
Abiraterone (Research or SOC)							
Prednisolone/ Prednisone (only if taken with abiraterone or docetaxel)							
Dexamethasone (only if taken with abiraterone or docetaxel)							
RT (Arm H only)							
Enzalutamide							
Metformin							
Transdermal Oestradiol							

CONCOMITANT MEDICATIONS AND TREATMENTS

Was the participant on any additional trial interventions or other treatments? (Any supportive care, RT for local disease control. Do not include treatment for SAE.)

21. ☐ 0 = No, ➪ Q29
1 = Yes, please give details below, continuing on a separate sheet if necessary

22. Treatment (use generic name)	23. Total Daily Dose	24. Route 1 = Oral 2 = Intravenous 3 = Subcutaneous 4 = Other	25. Start Date dd/mm/yyyy	26. Ongoing 0 = No 1 = Yes	27. End Date dd/mm/yyyy	28. Causal relationship to Serious Event 1 = Definitely 2 = Probably 3 = Possibly 4 = Unlikely 5 = Not related	29. Action taken due to Serious Event 0 = None 1 = Dose reduction 2 = Treatment delayed 3 = Treatment reduction and delayed 4 = Treatment stopped

*denotes the minimum information required for initial processing and review of SAE

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STAMPEDE SAE Form CRF

Event description

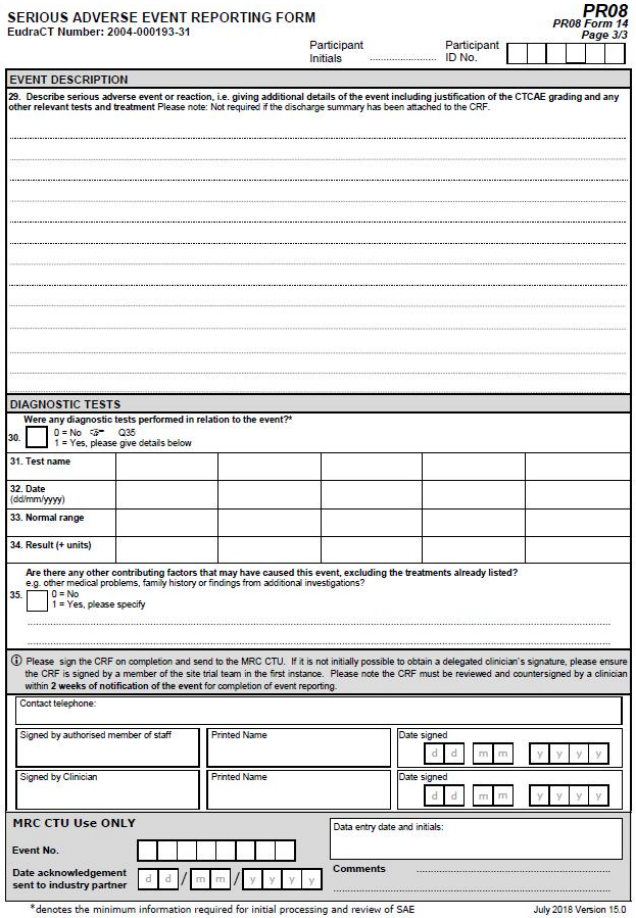
- Use this space to provide as much information as possible, regarding the event.
- Discharge summaries will be accepted in place of the event description

Diagnostic tests

- Ensure any tests carried out during the serious event are recorded here, for events such as Neutropenia include blood reports.

Signatures

- Authorised staff members can sign SAE forms in the initial instance, preventing the delay of submission.
- PI signature is required within 2 weeks of the initial submission of an event



SERIOUS ADVERSE EVENT REPORTING FORM
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Participant Initials ..... Participant ID No.

EVENT DESCRIPTION

29. Describe serious adverse event or reaction, i.e. giving additional details of the event including justification of the CTCAE grading and any other relevant tests and treatment Please note: Not required if the discharge summary has been attached to the CRF.

DIAGNOSTIC TESTS

30. Were any diagnostic tests performed in relation to the event?* 0 = No ☞ Q35 1 = Yes, please give details below

31. Test name						
32. Date (dd/mm/yyyy)						
33. Normal range						
34. Result (+ units)						

35. Are there any other contributing factors that may have caused this event, excluding the treatments already listed? e.g. other medical problems, family history or findings from additional investigations? 0 = No 1 = Yes, please specify

ⓘ Please sign the CRF on completion and send to the MRC CTU. If it is not initially possible to obtain a delegated clinician's signature, please ensure the CRF is signed by a member of the site trial team in the first instance. Please note the CRF must be reviewed and countersigned by a clinician within **2 weeks of notification of the event** for completion of event reporting.

Contact telephone:

Signed by authorised member of staff | Printed Name | Date signed (d d m m y y y y)

Signed by Clinician | Printed Name | Date signed (d d m m y y y y)

MRC CTU Use ONLY

Event No.

Date acknowledgement sent to industry partner (d d / m m / y y y y)

Data entry date and initials:

Comments .....

*denotes the minimum information required for initial processing and review of SAE

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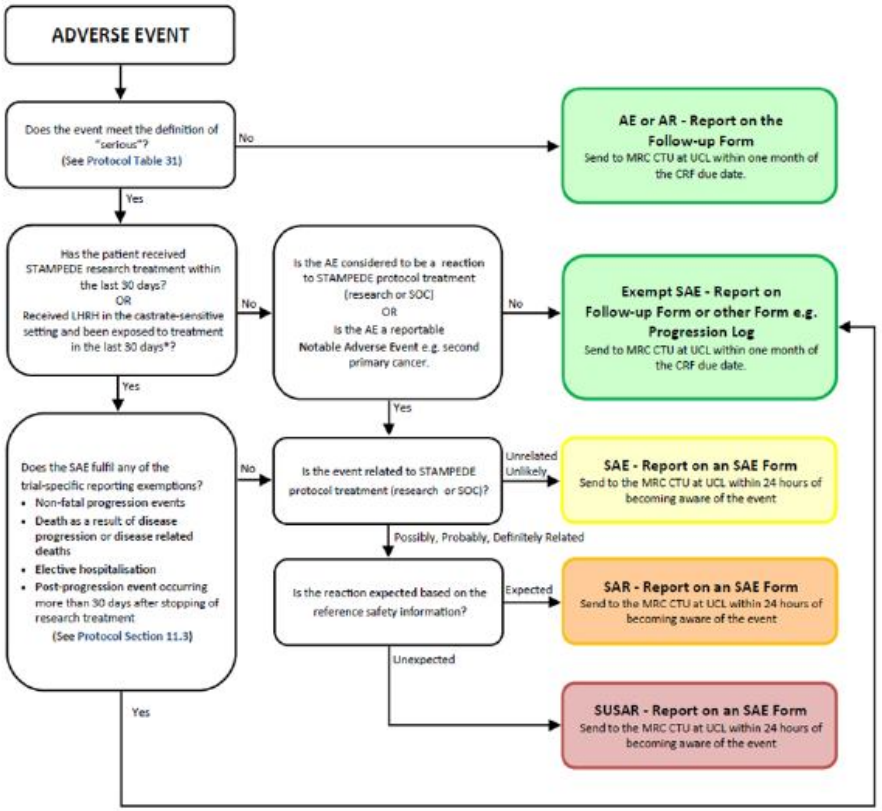
SAE Reporting Flowchart



**Exposure to LHRHa is assumed to be until the depot expiration date, therefore unrelated SAEs are reportable up until 8 weeks after the administration of a 4-week depot or 16 weeks after the administration of a 12-week depot.*

SAE Reporting Guidance

Protocol research treatments are the IMPs under investigation in STAMPEDE i.e. the additional or alternative treatments participants allocated to research arms (B-L) receive as part of the STAMPEDE protocol. Note, the research treatment in arm H (prostate RT) is not an IMP, but safety reporting requirements to the CTU are the same.

Protocol SOC treatments are standard forms of background treatment permitted as part of the STAMPEDE protocol

- Licenced ADT (e.g. LHRH analogues) given in the setting of castrate-sensitive prostate cancer (CSPC).
- Docetaxel given in castrate-sensitive prostate cancer

Please note standard forms of ADT e.g. LHRHa given in the setting of castrate-resistant prostate cancer (CRPC) is not considered protocol treatment

Non-protocol treatments are all prostate cancer treatments given following disease progression in the management of CRPC.

Reporting Timelines

AEs & ARs

- Are reported to the STAMPEDE team via the Toxicity CRF at each follow-up visit

SAEs & SARs & Other Important Medical Conditions

- Are reported to the STAMPEDE trial team within 24 hours of becoming aware of the event via the SAE form.
- The STAMPEDE team will provide an annual report of all SAEs to the MHRA.

SUSARs

- Are reported to the STAMPEDE trial team within 24 hours of becoming aware of the event via the SAE form.
- The STAMPEDE team will report these to the MHRA within 7 days of becoming aware of an event resulting in death or within 15 days of all other SUSARs

More Information

For more detailed information, please see the STAMPEDE protocol, the FAQ section of the website, or contact the trial team.

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