SERIOUS ADVERSE EVENTS DEFINITIONS AND REPORTING GUIDELINES Form # 13A

I. Serious Adverse Event: An SAE is defined as any undesirable experience meeting one or more of the following criteria, regardless of relatedness to study participation[1], occurring from the time a participant signs the informed consent (before the screening visit) until the end of the study[2,3,4].

1. **Resulting in Death**- all deaths (including cause of death) must be reported as SAEs.

2. **Hospitalization**- all hospitalizations, elective and non-elective, must be reported as SAEs. If a hospitalization is prolonged due to an event related to this study, this is also considered an SAE.

3. **Life-threatening**- if the patient is at substantial risk of dying at the time of the event, or if continued use of a study medication5 or study procedure6 would result in the patient's death. Included in this definition are potassium levels of >6.5 mEq/L, and doubling of baseline serum creatinine within 12 weeks of beginning study medications.

4. **Resulting in significant, persistent or permanent harm or disability.**

5. **Exceeding the nature, severity or frequency of risk described in the protocol.**

6. **Congenital anomaly**- if there is suspicion that exposure to a study medication[5] or procedure[6] prior to conception or during pregnancy resulted in an adverse outcome in the child.

7. Abuse of, or dependency on, study medication[5].

8. Any other important medical event, including new cancer diagnosis, which may jeopardize the participant, or may require intervention to prevent permanent impairment or damage or other outcome listed above.

[1] An event is "reasonably related to study participation" if it is or could reasonably be the result of or exacerbated by the use of study medication, whether masked or open-label, or any study procedure. While all SAEs are to be reported per the guidelines above, only those that are reasonably related to study participation will be counted as primary or secondary outcomes.
[2] The "end of the study" is defined as the "stopping date" or "x date," and not the "end of data close-out."
[3] Data analysis will separate out any SAEs occurring before the start of study medication from those occurring after.
[4] For the HALT PKD study, all serious adverse events that are reasonably related to study participation are, by virtue of their seriousness, unanticipated events which are not consistent with the risk information described in the protocol. Events are considered unanticipated by virtue of greater specificity (type or nature of an event) or greater severity (degree, frequency or outcome of an event; of a greater intensity than what has been previously observed). Examples of the latter: hypokalemia is an expected event, but cardiac arrest is unanticipated. Hypotension causing lightheadedness is an expected event, but a syncopal spell causing a trip to the ER for "fall" is unanticipated.
[5] The term "study medication" is defined as any medication, masked or open-label, used to control blood pressure from the time a participant signs consent until the end of the study, even if the participant has withdrawn consent to continue in the study.
[6] A "study procedure" is any test or procedure required for the study (e.g., MRI for study A).

II. **Reporting Requirements:** All SAEs must be reported within 24 hours of study personnel learning of the event to the local PI and to the DCC via data entry of SAE Report Form 13. Information not available at the time of the initial report should be submitted to the DCC as a follow-up report within 5 business days. All SAEs will be reported using the National Cancer Institute's Common Terminology Criteria for Adverse Events
(CTCAE version 3.0) and MedDra codes (version 6.0) which have been mapped to the CTCAE. Reporting requirements for the FDA differ depending on their relatedness to study interventions as follows:

<u>SAEs that are reasonably related to study participation[1]:</u>

Unanticipated: The DCC will notify NIDDK of SAEs that are drug-related and unanticipated within one business day of receiving the report, and provide safety reports to all PIs and the DSMB within five business days (annually if anticipated). NIDDK will report drug-related and unanticipated SAEs to the FDA within seven days of initial knowledge of the event.

Anticipated: The DCC will report *anticipated* SAEs to the FDA annually, but these may need to be reported in a more timely fashion to local IRBs (usually 7 days but see local policy). PIs at the clinical centers are responsible for fulfilling local IRB reporting requirements, which may vary by center.

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SAEs that are unrelated to study participation, *with the exception of death, hospitalization, and lifethreatening events:*

The DCC will prepare summary annual reports for the clinical centers, NIDDK, DSMB and FDA. PIs at the clinical centers are responsible for fulfilling local IRB reporting requirements, which may vary by center. *All deaths, hospitalizations, and life-threatening events,* whether related to study participation or not, must be reported as above.

SAEs that are related to study participation but are not related to study drug:

Some PCCs may require study-related, but not drug-related, SAEs (e.g., hypotension leading to fall) to be reported to their local IRB (usually within 7 days but see local policy). PIs at the clinical centers are responsible for fulfilling local IRB reporting requirements, which may vary by institution.

Reporting from PCC to DCC: **An event is serious if it is or results in**	**Study Related**	Report to PI & DCC (Form 13)	**Report to local IRB** (may vary by site)
Death or Hospitalization	Yes	24 hrs	5 business days
	No	24 hrs	5 business days
Life-threatening, Resulting in permanent disability, Requiring Intervention to prevent impairment, Exceeding nature, severity, or Frequency described in protocol, Congenital Anomaly	Yes	24 hrs	5 business days
	No	24 hrs	Annually

Reporting by the DCC to:	**NIDDK**	**PI → IRB#**	**DSMB**	**FDA**
Study Related SAEs	1 business day*	5 business days	5 business days	% *
Unrelated SAEs	Annual Summary	Annual Summary	Annual Summary	%

* SAEs that are both drug-related and unanticipated: NIDDK will report to FDA within 7 days of initial knowledge.
% Expected SAEs and those that are both unanticipated and unrelated to drug: DCC submits annual summary reports to FDA.
# PIs are responsible for reporting SAEs to local IRBs per site-specific guidelines.

1. Staff at the PCC where the event occurs will report all SAEs to the DCC within 24 hours of learning of the event, and report it to their IRB per institutional guidelines.
2. DCC reviews SAE report and sends electronic notification to Boehringer Ingelheim by the end of the next business day, or within 24 hours if the report is received before a weekend or holiday.
3. DCC reviews SAE report and sends electronic notification to all PCCs (including the reporting PCC) within five days of the original report with a reminder of their responsibilities for reporting.
4. PIs at all other PCCs (where the event did not occur) are responsible for reporting the event to their IRB per institutional guidelines.
5. DCC Reports to NIDDK and DSMB per the table above (Table 10, in section 12 of the protocol).
6. DCC reports events to the FDA as listed in the table below.

Event	**Anticipated/Unanticipated?**	**FDA Reporting Requirement**
Study- **AND** Drug- Related	Anticipated/Expected	Annual Report
Study- **AND** Drug- Related	Unanticipated	NIDDK reports to FDA within 7 days of initial knowledge
Study-Related **BUT** unrelated to drug	Anticipated/Expected	Annual Report
Study-Related **BUT** unrelated to drug	Unanticipated	Annual Report
Unrelated to Study	N/A	N/A

III. Patient Management: The need to discontinue or modify the dose of the medication will be left to the discretion of the PI. Unblinding of study group assignment will occur only if there is a pregnancy or another unusual circumstance, but it is not anticipated for most SAEs.