Investigators' Responsibility for Safety and Serious Adverse Events

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Investigators'Responsibilities

- **Complete understanding of the protocol, including inclusion/exclusion criteria, visit times, schedule of procedures, and profile of study drug**
- **Recruitment and Retention—know what is expected and how you are doing**
  - **Your research subjects should know who you are and be comfortable contacting you for questions**
  - **Both recruitment and retention will be better if you are actively involved**

Investigators' Study Management Responsibilities

- **Overall management of the study including oversight of patient safety**
  - **Regular meetings with study team (at least weekly during heavy recruitment periods)**
  - **Generous availability to study staff (especially the coordinator) to answer questions and address and classify adverse events**
  - **Know who your research subjects are so that you can assist your staff in maintaining rapport with subjects**

Adverse Event Reporting

An AE is any untoward, unfavorable, or unintended medical occurrence (including symptoms, physical sign, lab finding or disease) observed in or experienced by a participant that is not a benefit to the participant whether or not it is considered study-related.

Adverse Event Reporting

AEs will be documented in the eCRF and characterized by:

- **Seriousness**
- **Expectedness**
- **Relatedness**
- **Action taken**
- **Severity**
- **Frequency**
- **Outcome**

Serious Adverse Event Reporting

- **Death**
- **Life threatening condition**
- **New inpatient hospitalization or prolongation of existing hospitalization**
- **Persistent or significant disability or incapacity**
- **Congenital anomaly/birth defect**
- **Any other significant hazard that may jeopardize the participant's health or require medical or surgical intervention to prevent one of the outcomes listed previously**

What is Life Threatening?

- **An event that in the view of the investigator places the patient or subject at immediate risk of death or**
- **Requires medical or surgical intervention to prevent one of the outcomes listed previously**
- **Not an event that had it occurred in a more severe form might have caused death**

How to Define Expected?

- **Must decide if the event is "expected" or not.**
- **An Expected Event is:**
  - **Is described in current protocol or informed consents**
  - **Is expected as the natural progression of any underlying disease, disorder, or**
  - **Is consistent with the subject(s) age and predisposing risk factor profile**
  - **Is expected in terms of nature, severity, or frequency**

D2d Expected Events

- Hypercalcemia
- Hypercalcuria
- Hyperphosphatemia
- Nephrolithiasis
- Nephrotoxicity
- Anemia
- Polyuria
- Nausea
- Poor appetite
- Weakness
- Fatigue
- Insomnia
- Headache
- Metallic taste
- Bruising/discomfort
- Syncope
- Skin infection/phlebitis
- Nausea/vomiting
- Hypoglycemia post glucose load
- Mild anemia

What about Relationship?

- **Must determine relationship to study intervention. In your best judgment is the event :**
  - **Not related**
  - **Possibly, probably or definitely related**

- **“Possibly related” means there is a reasonable possibility that the event may have been caused by the procedures or interventions involved in the research**

Investigators' Responsibilities Serious Adverse Events

- **Rapid reporting response for Serious Adverse Events.**
  - **Ensuring that the situation as summarized by your staff makes medical sense and is not missing essential information**
  - **Personally contacting "elsewhere general" to obtain clinical information as needed**
  - **Adhering to timelines for reporting SAEs**
  - **SAEs must be reported ASAP but always within 5 business days (by filling out the eCRF AE form and classifying the event as serious). Classifying the event as serious will send an alert to the Coordinating Center and the Safety Outcomes Chair.**

D2d-Unanticipated Problem (UAP)

An UAP is defined as any adverse event, incident, experience or outcome that meets *ALL* of the following criteria:

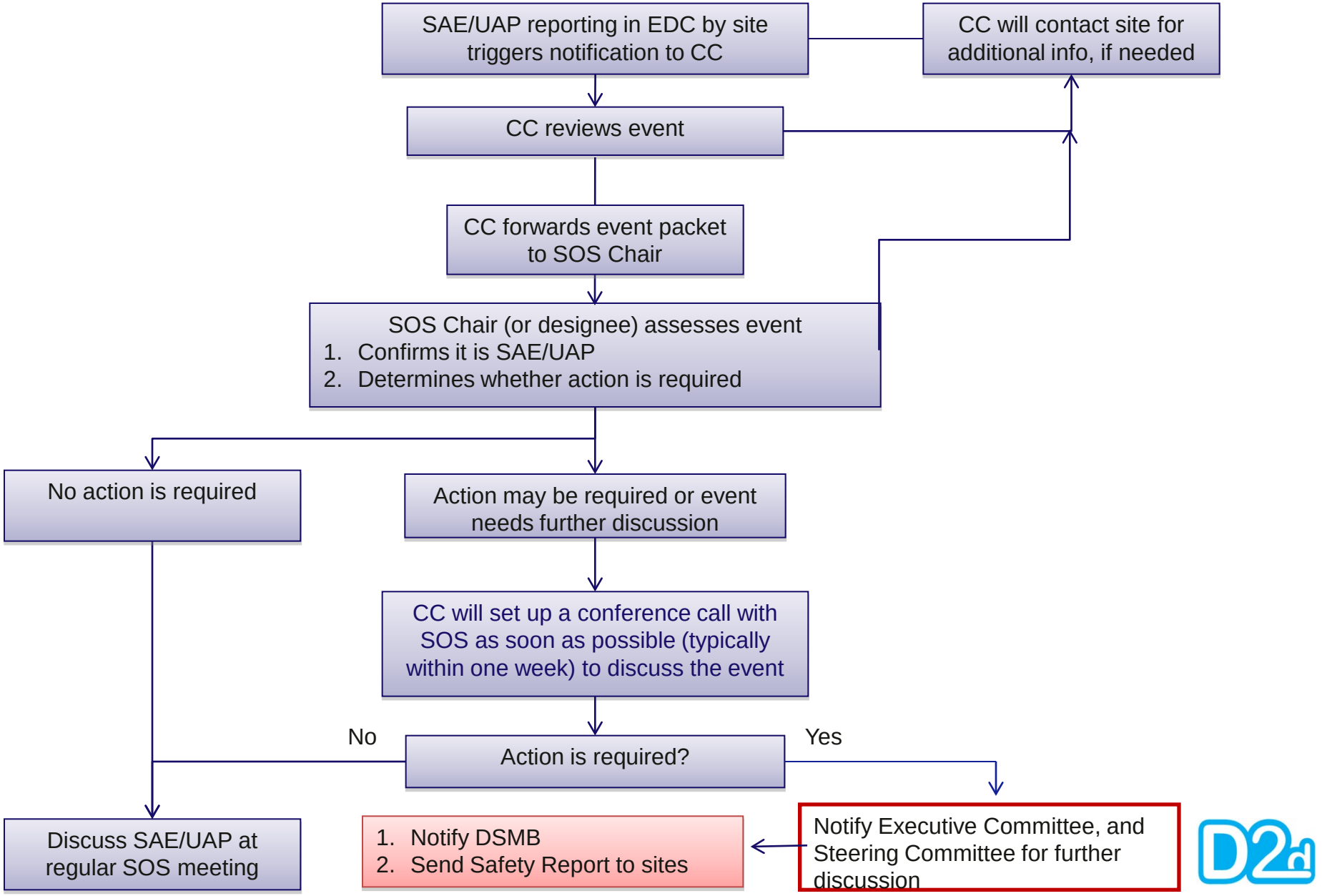
1. **Unexpected in terms of nature, severity or frequency**
2. **Possibly, probably or definitely related to participation in the research**
3. ***Suggests that the research places participants or others at a greater risk of harm than previously recognized.***

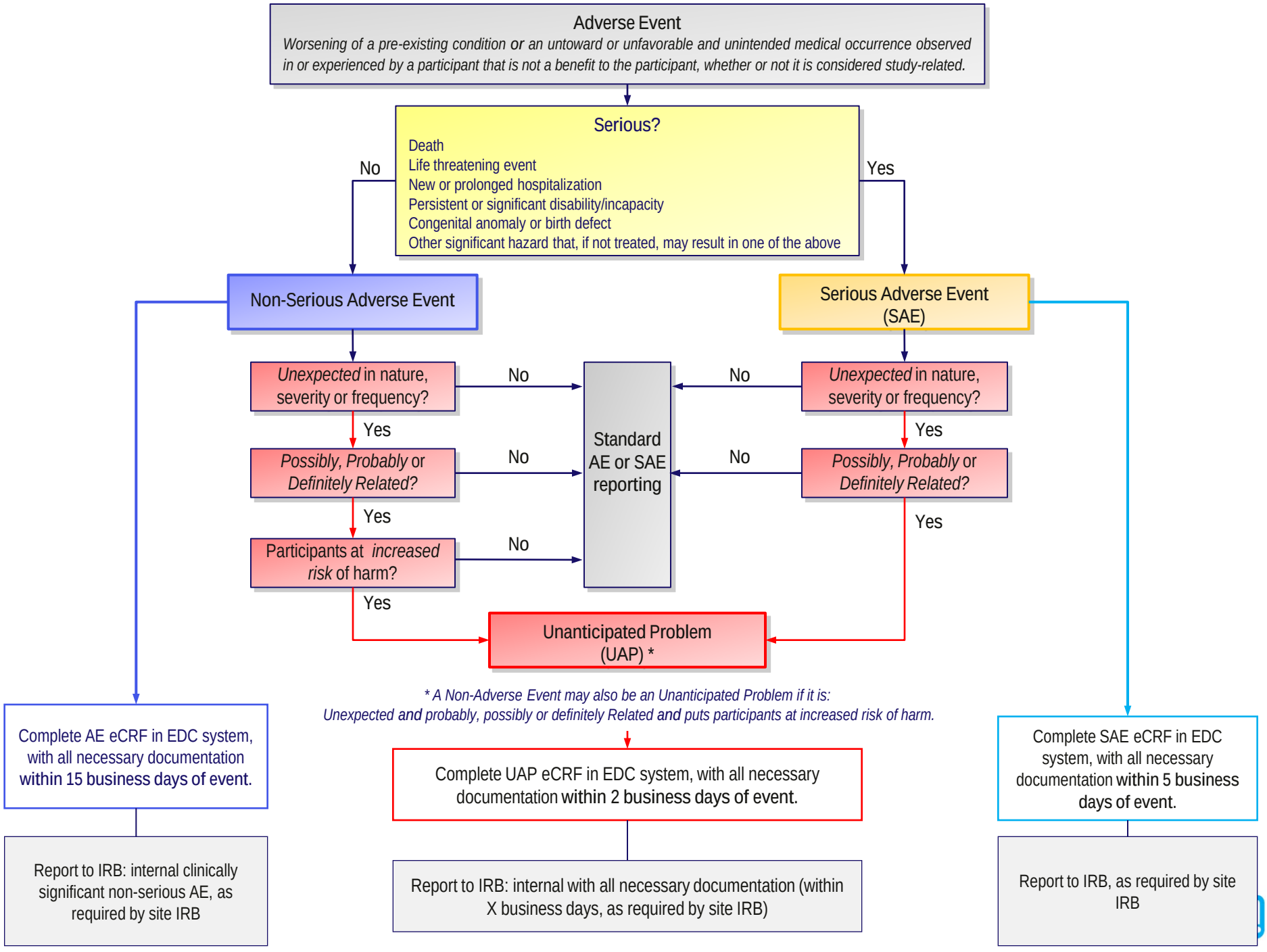
D2d-Unanticipated Problem (UAP)

- **UAP usually require specific action such as modification of the protocol or suspension of recruitment**

- ***UAPs must be reported ASAP but always within 2 business days!***

D2d SOS procedure

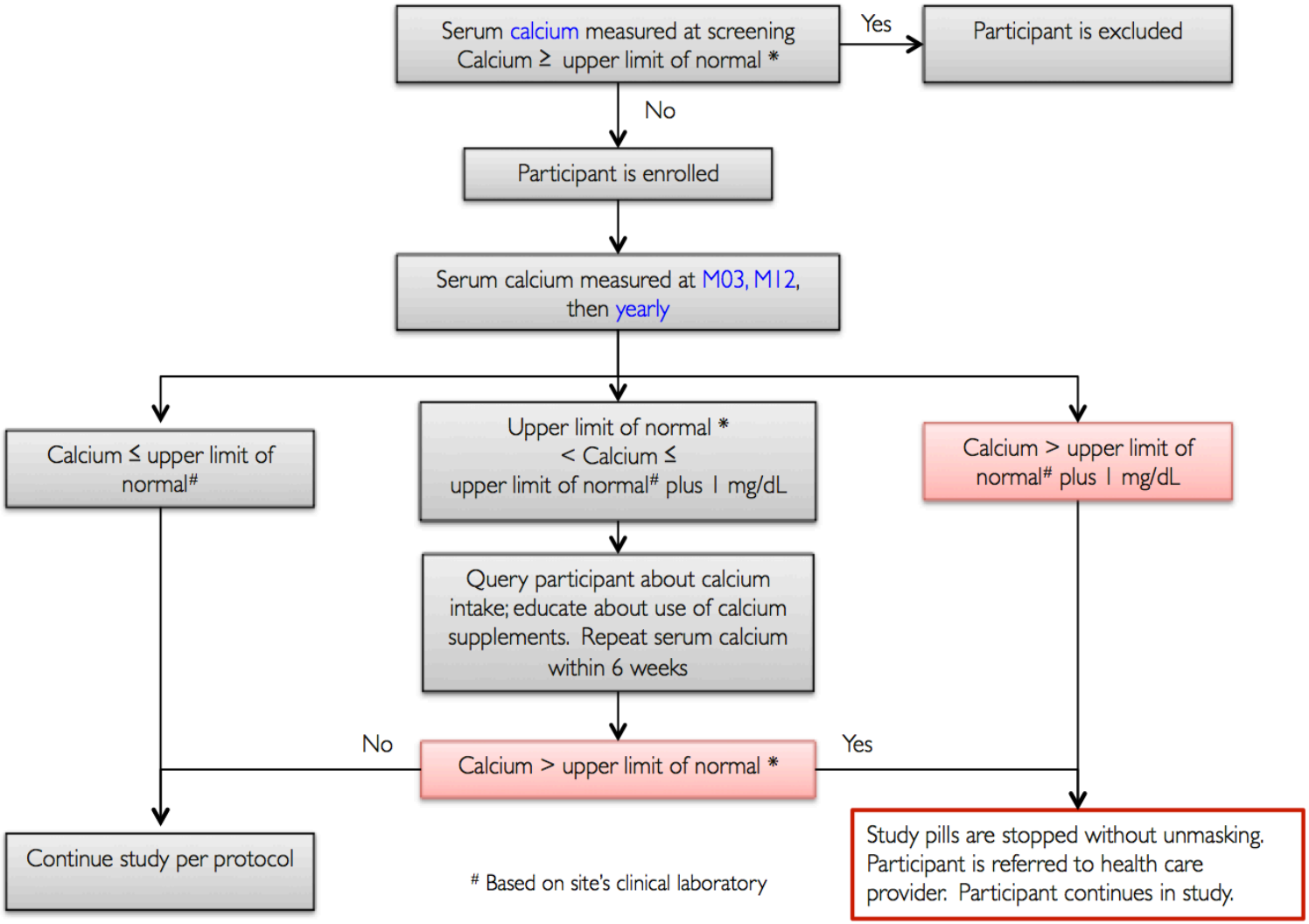



Adverse Event
Worsening of a pre-existing condition or an untoward or unfavorable and unintended medical occurrence observed in or experienced by a participant that is not a benefit to the participant, whether or not it is considered study-related.
Serious?
Death
Life threatening event
New or prolonged hospitalization
Persistent or significant disability/incapacity
Congenital anomaly or birth defect
Other significant hazard that, if not treated, may result in one of the above
No
Yes
Non-Serious Adverse Event
Serious Adverse Event (SAE)
Unexpected in nature, severity or frequency?
Possibly, Probably or Definitely Related?
Participants at increased risk of harm?
Standard AE or SAE reporting
Unanticipated Problem (UAP) *
* A Non-Adverse Event may also be an Unanticipated Problem if it is:
Unexpected and probably, possibly or definitely Related and puts participants at increased risk of harm.
Complete AE eCRF in EDC system, with all necessary documentation within 15 business days of event.
Report to IRB: internal clinically significant non-serious AE, as required by site IRB
Complete UAP eCRF in EDC system, with all necessary documentation within 2 business days of event.
Report to IRB: internal with all necessary documentation (within X business days, as required by site IRB)
Complete SAE eCRF in EDC system, with all necessary documentation within 5 business days of event.
Report to IRB, as required by site IRB

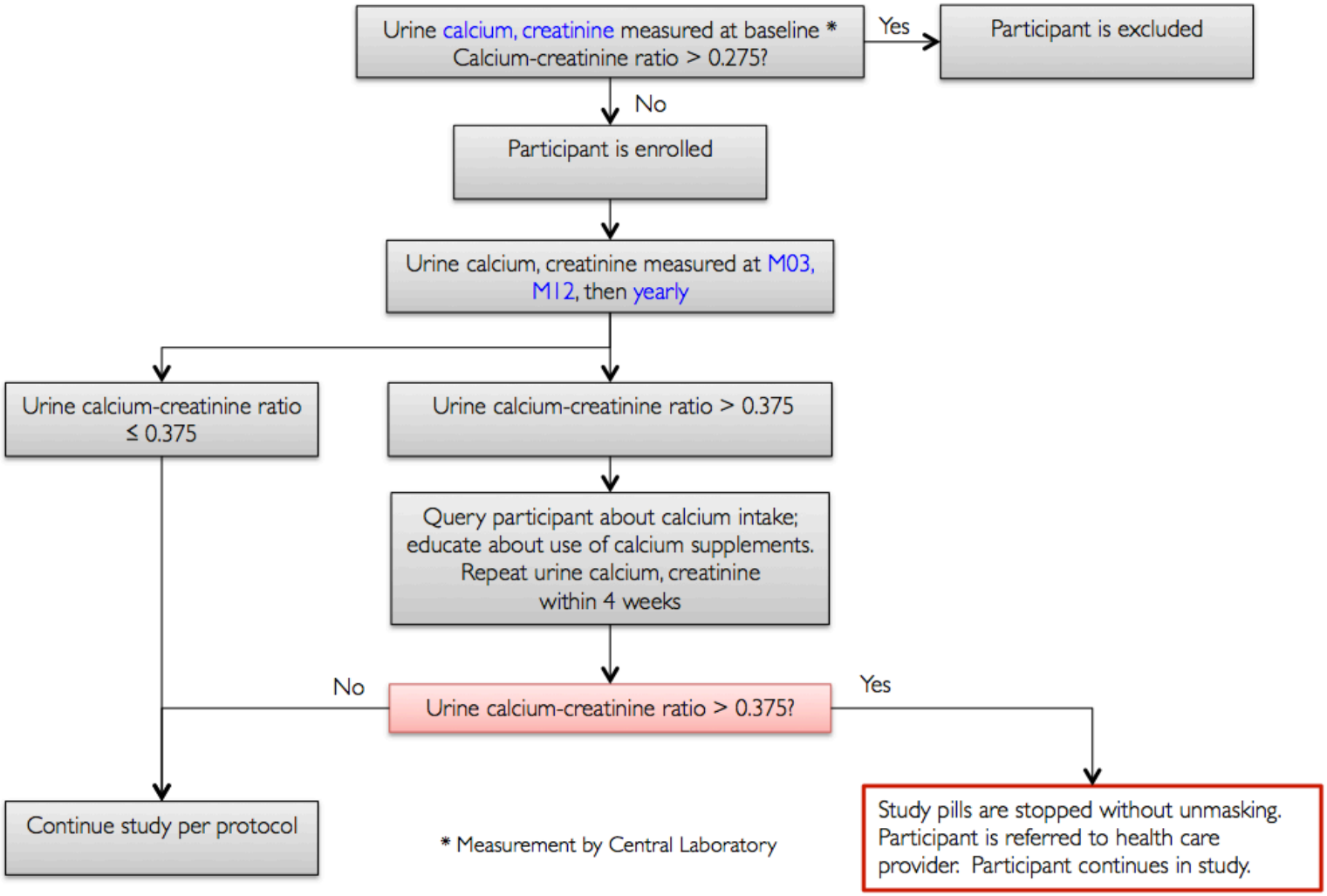
D2d specific monitoring

- Hypercalcemia
- Hypercalcuria
- Reduced kidney function
- Pregnancy

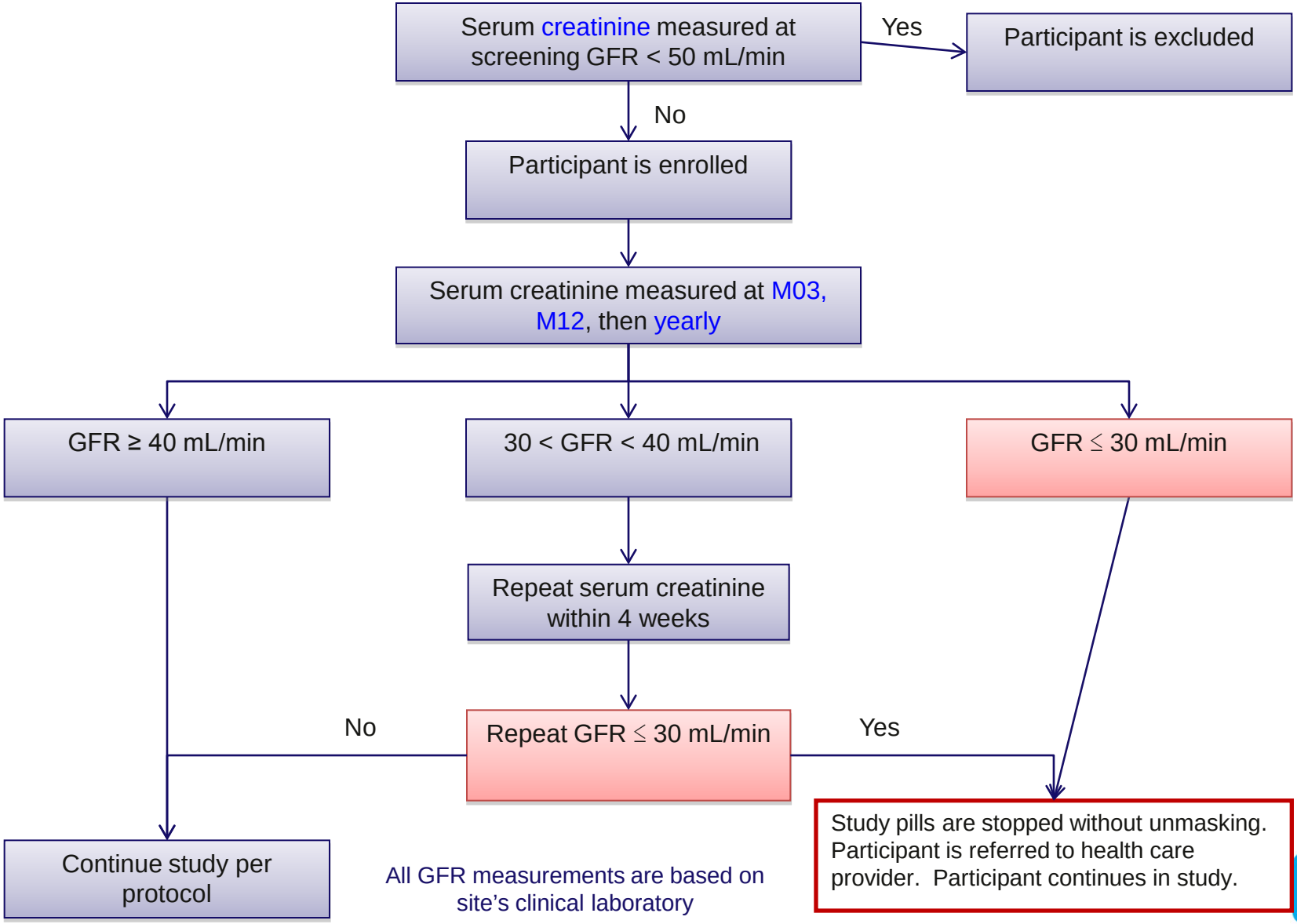
Hypercalcemia



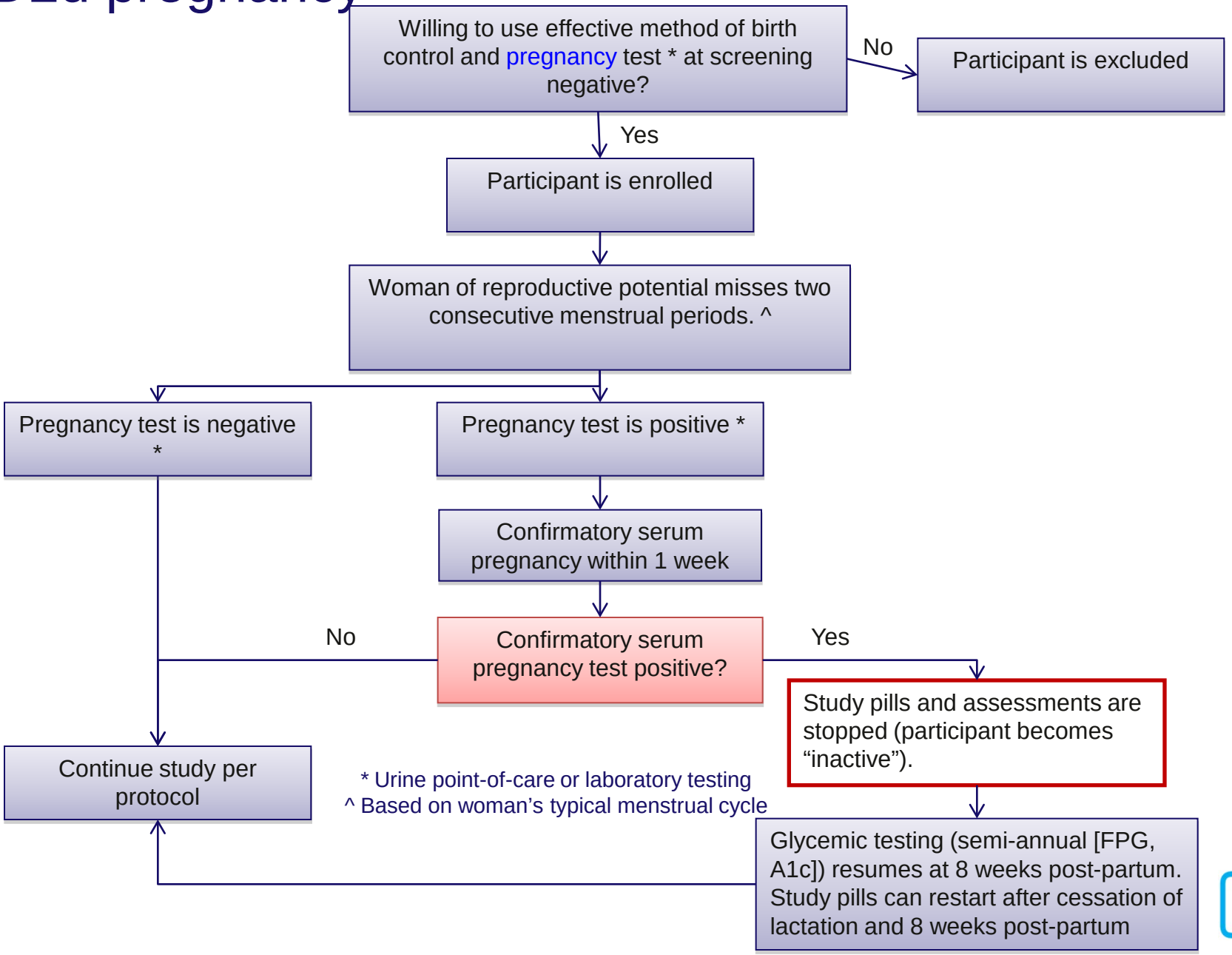
Hypercalcuria



Kidney function



D2d pregnancy



Summary

- Beyond the usual definition of SAE, there are D2d study specific events that need attention
- You (the site PI) are responsible for all issues of patient safety including determining if an event is Expected or Unexpected and its Relationship to study intervention
- BE Involved! BE Available!

Homework for Site PIs

- Contact your institutions Public Relations Office and let them know about the D2d study and the upcoming press release.
- NIDDK's Office of Communication and Public Liaison contact is:

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  301-496-3583

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