STANDARDS FOR IMAGING ENDPOINTS AND MANUFACTURING OF PET RADIOPHARMACEUTICAL PRODUCTS IN CLINICAL TRIALS

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Image Interpretation: Discussion Points

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Question 1

(A) Please comment on the challenges posed by large-scale, multi-center national clinical trials, how on-site/investigator parameters are standardized, and how results are managed.

(B) Please address potential issues of discordance between site and central reads and the management of these issues. In addition, please provide examples of management of these trials including image interpretation aspects by various organizations.

1A. Challenges posed by large-scale, multi-center national clinical trials / on-site parameter standardization

- Necessity for both central and local reads: Guidance will need to address issues for both.
- Differential control: Amount of control is different between the core and local sites.
- Training of local readers: On-site readers need training on the protocol specific for each clinical trial.
- Separate tasks: Trial reads and clinical reads may require that different information be recorded.

1B. Discordance between local and central reads

- **Predictive ability of discordance:** Discordance between local and central reads at a single time point may not be predictive of discordance across all time points.

Question 2

Please discuss and prioritize approaches to reduce image interpretation variability in clinical trials (e.g., the need for standardization of software, software tool standards and onsite electronic data capture) and note which of these approaches are the most practical to implement. Discuss the appropriate management of clinical data in trials that use imaging results as an endpoint.

2A. Approaches to reduce image interpretation variability in clinical trials (p1 of 2)

- **Site capabilities:** Essential to understand the imaging and imaging interpretation capabilities at each site.
- **Pilot testing:** Useful (Phase 1 or 2 trial).
- **Manuals:** Specifying how to perform measurements, selection rules, stopping rules, etc.
- **Same reader:** Ideal to have same reader interpret images at every timepoint for each subject, but may not be practical.

2A. Approaches to reduce image interpretation variability in clinical trials (p2 of 2)

- Reader selection: Debatable whether measurements and reads can be performed by

  (a) radiologist only (as final arbiter) vs.

  (b) other qualified professional

- Time of target lesion selection: At baseline or when follow-up study is read? The latter reduces variability but may add bias.

2B. Software standardization

- **Within vs across study:** Appropriate to standardize software within a study. Standardizing across studies may hinder innovation.

- **Implementation:** Difficult to implement standardized software in multinational trials at this time.

Question 3

(A) What is the role of the report (and image annotations) performed by the radiologist rendering the official reading? How does this relate to the on-site reads of the study team? If there are discrepancies, how should this be addressed?

(B) Is it possible to develop a standard CRF that is applicable to most clinical trials that use imaging or to develop a CRF that may be used by both on-site and central readers?

3A. Role of the report

- Source of local CRF info: Information from clinical reports should not be transferred onto CRFs, particularly if the transfer is performed by a person other than the one generating the report.

- Keeping the clinical read separate: Debatable whether the clinical report should be made inaccessible to clinical trial readers.

- Specifying the lexicon: Issue of whether the guidance should specify the lexicon was raised. Whether to use a lexicon and which lexicon may be trial dependent.

3B. Standard CRF

- Single CRF unrealistic: One CRF for both clinical read and trial reads may be unrealistic and probably not appropriate. Ways for unifying content is up for brainstorming.

- Tailoring the CRF: Perhaps CRF should be tailored to the clinical trial context.

- Specifying the minimum required info: The guidance should specify the information that is absolutely required on the CRF.

Other Discussion

- Need to obtain buy-in of local radiologists into clinical trials – will require adequate compensation and/or allocated time in order to complete trial activities that are above and beyond routine clinical practice.
- In the end, the guidance should be Contact-specific and Phase dependent