2018 ISCTM Spring Meeting (Feb 20-22, Washington DC)

Estimands and Missing Data Working Group – Feb 20 2018 Meeting Minutes:

- The meeting was initiated by Pilar Lim (Janssen R&D, WG co-chair), who welcomed everyone present and invited all attendees to introduce themselves.

- Frank Pétavy (EMA, member of the ICH E9(R1) Expert Working Group) provided an update on the draft ICH E9(R1) Addendum. All comments across regulatory agencies are expected to be received by June 2018. The ICH E9(R1) Expert Working Group is expecting 2-3 meetings to go through the received comments and to potentially finalize this guidance by the end of 2019. At regulatory meetings such as End of Phase 2, more questions or proposals are expected on the estimands of the discussed studies. The trial planning framework of the ICH E9(R1) is also being incorporated in disease related guidelines, such the EMA draft diabetes guideline http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/02/WC500243464.pdf (see Section 4.2.1).

- Elena Polverejan (Janssen R&D, WG co-chair) presented the background of the trial planning framework recommended by the ICH E9(R1). The slides used in the discussion are to be made available to all WG members as well as the attendees of the Feb 20 meeting. The discussion topics included:

    - It was recognized that, while it is recommended for the estimands not to include specifications on their estimators, it is difficult to separate considering the estimand vs the analysis. The process of defining an estimand is iterative, considerations on estimators leading to updates on the estimand. The estimators are not a distraction and they constitute a useful and clarifying part of the process of selecting different strategies for different IEs when defining an estimand.

    - How the teams should deal with protocol violators, such as subjects who lie in their PRO responses? They can be specified as an intercurrent event (IE) only if they can be identified (e.g. treatment non-compliers could be identified by the PK measure of the drug in the body). There is no universal rule on the strategy to be used for this type of IE.

    - There could be many IEs that could be considered for an estimand. Teams should discuss the IEs expected to have most impact on the treatment effect. It is important however to start with a comprehensive list of potential IEs.

    - One study could have multiple estimands if the considered design could accommodate all. Different stakeholders could be interested in different estimands. For example, regulatory stakeholders could be interested in the existence of an overall treatment effect in all subjects. Prescribers could be interested in the treatment effect had the subjects continued the treatment for a certain time period. Payers could be interested in the treatment effect in the subjects who are adherent to the drug for a long period.

    - The composite strategy should be used with caution. In depression subjects might discontinue treatment because they feel better.

- While study discontinuation is an IE on its own, its strategy differs from the treatment discontinuation strategy only if the chosen strategy for treatment discontinuation is the treatment policy.

Many thanks to the members of this working group and to all attendees for a great interactive meeting!