Appendix 2

Original statements for each PRO variable of interest presented as condensed summary statements

In Chapter 4 of the guidebook a condensed summary statement is listed for the intercurrent events i) disease progression, ii) deviation from protocol defined treatment and iii) concomitant therapies allowed by the protocol. The original statements for each PRO variable of interest is listed below.

1d. Handling of intercurrent events

i Disease progression

ICEdisprog1_RCT

Statement: when the goal of the PRO objective is to draw conclusions about clinical benefit (confirmatory objective) using magnitude of PRO (change) score at time *t* for a specific PRO domain: if a patient's disease progresses before time *t*, the main PRO analysis technique would be to use the PRO scores collected after disease progression in the analysis at time *t*. Any deviations should be justified.

An overview of relevant ICEs should be reported and discussed to assess to what extent those ICEs could have impacted the PRO results. This may be supported by supplementary/ sensitivity analyses.

Explanation: if the PRO objective is confirmatory, it is important to preserve the ITT and safety population by collecting PROs after disease progression (as long as the patient remains on study) and to use this data in the analysis. Disease progression can be an unavoidable event that may occur whilst treatments are compared. Therefore, PRO scores collected after the occurrence of such ICEs should be used in the main analysis. When defining the estimand, the feasibility and usefulness (in light of the research objectives) of collecting post-progression

data should be taken into account. When such data is not collected, this should be justified. Sensitivity analyses may also be employed, where appropriate, to mitigate the effects of (partially) missing post-progression data.

An overview and reporting of relevant ICEs should help clarify to what extent those ICEs could have impacted the PRO results. Hence, reporting of ICEs is not requested for ICEs occurring after time *t* nor for ICEs that are disregarded for analyses. If the PRO objective is limited to estimating while-on-treatment scores, then data collection can be stopped when protocol treatment discontinuation coincides with progression.

Example: the main goal is to compare specific PRO scores at month six between two treatment arms, but that patient's disease progressed at month four. The patient remained in the study after disease progression, and PRO data were collected for that patient at month six. PRO scores for that patient collected at month six must be used in the analysis regardless of the progression.

ICEdisprog2_RCT

Statement: when the goal of the PRO objective is to draw conclusions about clinical benefit (confirmatory objective) using time-to-improvement within a time frame for a specific PRO domain: if a patient's disease progresses before the PRO improvement occurs, the main PRO analysis technique would be to use the PRO scores collected after disease progression to determine whether or not a PRO improvement occurred. Any deviations should be justified.

An overview of relevant ICEs should be reported and discussed to assess to what extent those ICEs could have impacted the PRO results. This may be supported by supplementary/ sensitivity analyses.

Alternative ICE strategies might be considered as supplementary analyses to explore the robustness of outcomes and inform about the potential of bias.

Explanation: if the PRO objective is confirmatory, it is important to preserve the ITT and safety population by collecting PROs after disease progression (as long as the patient remains on study) and to use this data in the analysis. Disease progression can be an unavoidable event that may occur whilst treatments are compared. Therefore, PRO scores collected after the occurrence of such ICEs should be used in the main analysis. When defining the estimand, the feasibility and usefulness (in light of the research objectives) of collecting post-progression data should be taken into account. When such data is not collected, this should be justified. Sensitivity analyses may also be employed, where appropriate, to mitigate the effects of (partially) missing post-progression data.

An overview and reporting of relevant ICEs should help clarify to what extent those ICEs could have impacted the PRO results. Hence, reporting of ICEs is not requested for ICEs occurring after the PRO deterioration event nor for ICEs that are disregarded for analyses. If the PRO objective is limited to estimating while-on-treatment scores, then data collection can be stopped when protocol treatment discontinuation coincides with progression.

Example: the main goal is to compare time-to-improvement in a specific PRO domain between two treatment arms within a pre-specified time frame. The patient's disease progressed before a PRO improvement was observed, and the patient remained in the study. PRO scores for that patient collected after progression must be used in the analysis regardless of the progression to determine whether a PRO improvement would be observed within the pre-specified time frame.

ICEdisprog3_RCT

Statement: when the goal of the PRO objective is to draw conclusions about clinical benefit (confirmatory objective) using time-to-deterioration within a time frame for a specific PRO domain: if a patient's disease progresses before the PRO deterioration occurs, the main PRO analysis technique would be to use the PRO scores collected after disease progression to determine whether or not a PRO deterioration occurred. Any deviations should be justified.

An overview of relevant ICEs should be reported and discussed to assess to what extent those ICEs could have impacted the PRO results. This may be supported by supplementary/ sensitivity analyses.

Explanation: if the PRO objective is confirmatory, it is important to preserve the ITT and safety population by collecting PROs after disease progression (as long as the patient remains on study) and to use this data in the analysis. Disease progression can be an unavoidable event that may occur whilst treatments are compared. Therefore, PRO scores collected after the occurrence of such ICEs should be used in the main analysis. When defining the estimand, the feasibility and usefulness (in light of the research objectives) of collecting post-progression data should be taken into account. When such data is not collected, this should be justified. Sensitivity analyses may also be employed, where appropriate, to mitigate the effects of (partially) missing post-progression data.

An overview and reporting of relevant ICEs should help clarify to what extent those ICEs could have impacted the PRO results. Hence, reporting of ICEs is not requested for ICEs occurring after the PRO deterioration event nor for ICEs that are disregarded for analyses. If the PRO objective is limited to estimating while-on-treatment scores, then data collection can be stopped when protocol treatment discontinuation coincides with progression.

Example: the main goal is to compare time-to-deterioration in a specific PRO domain between two treatment arms within a pre-specified time frame. The patient's disease progressed before a PRO deterioration event was observed and remained on study. PRO scores for that patient collected after progression must be used in the analysis regardless of the progression to determine whether a PRO deterioration would be observed within the pre-specified time frame.

ICEdisprog4_RCT

Statement: when the goal of the PRO objective is to draw conclusions about clinical benefit (confirmatory objective) using responder improvement at time *t* for a specific PRO domain:

if a patient's disease progresses before time *t*, the main PRO analysis technique would be to use the PRO scores collected after disease progression in the analysis at time *t*. Any deviations should be justified.

An overview of relevant ICEs should be reported and discussed to assess to what extent those ICEs could have impacted the PRO results. This may be supported by supplementary/ sensitivity analyses.

Alternative ICE strategies might be considered as supplementary analyses to explore the robustness of outcomes and inform about the potential of bias.

Explanation: if the PRO objective is confirmatory, it is important to preserve the ITT and safety population by collecting PROs after disease progression (as long as the patient remains on study) and to use this data in the analysis. Disease progression can be an unavoidable event that may occur whilst treatments are compared. Therefore, PRO scores collected after the occurrence of such ICEs should be used in the main analysis. When defining the estimand, the feasibility and usefulness (in light of the research objectives) of collecting post-progression data should be taken into account. When such data is not collected, this should be justified. Sensitivity analyses may also be employed, where appropriate, to mitigate the effects of (partially) missing post-progression data.

An overview and reporting of relevant ICEs should help clarify to what extent those ICEs could have impacted the PRO results. Hence, reporting of ICEs is not requested for ICEs occurring after time *t* nor for ICEs that are disregarded for analyses. If the PRO objective is limited to estimating while-on-treatment scores, then data collection can be stopped when protocol treatment discontinuation coincides with progression.

Example: the main goal is to compare the ratio of patients displaying improvement in PRO scores at month six for a specific domain (e.g. pain) between two treatment arms, but a patient's disease progressed at month four. PRO scores for that patient collected at month six and must be used in the analysis regardless of the progression.

ICEdisprog5_RCT

Statement: when the goal of the PRO objective is to draw conclusions about clinical benefit (confirmatory objective) using responder deterioration at time *t* for a specific PRO domain: if a patient's disease progresses before time *t*, the main PRO analysis technique would be to use the PRO scores collected after disease progression in the analysis at time *t*. Any deviations should be justified.

An overview of relevant ICEs should be reported and discussed to assess to what extent those ICEs could have impacted the PRO results. This may be supported by supplementary/ sensitivity analyses.

Alternative ICE strategies might be considered as supplementary analyses to explore the robustness of outcomes and inform about the potential of bias.

Explanation: if the PRO objective is confirmatory, it is important to preserve the ITT and safety population by collecting PROs after disease progression (as long as the patient remains on study) and to use this data in the analysis. Disease progression can be an unavoidable event that may occur whilst treatments are compared. Therefore, PRO scores collected after the occurrence of such ICEs should be used in the main analysis. When defining the estimand, the feasibility and usefulness (in light of the research objectives) of collecting post-progression data should be taken into account. When such data is not collected, this should be justified. Sensitivity analyses may also be employed, where appropriate, to mitigate the effects of (partially) missing post-progression data.

An overview and reporting of relevant ICEs should help clarify to what extent those ICEs could have impacted the PRO results. Hence, reporting of ICEs is not requested for ICEs occurring after time *t* nor for ICEs that are disregarded for analyses. If the PRO objective is limited to estimating while-on-treatment scores, then data collection can be stopped when protocol treatment discontinuation coincides with progression.

Example: the main goal is to compare the ratio of patients displaying deterioration in PRO scores at month six for a specific PRO domain (e.g. pain) between two treatment arms, but a patient's disease progressed at month four. PRO scores for that patient collected at month six must be used in the analyses regardless of the progression.

ii. Deviation from protocol defined treatment

ICEprodev1_RCT

Statement: when the goal of the PRO objective is to draw conclusions about clinical benefit (confirmatory objective) using magnitude of PRO (change) score at time *t* for a specific PRO domain: if a patient deviated from protocol-defined treatment before time *t* (not causing treatment discontinuation), the main PRO analysis technique would be to use the PRO scores collected after deviation from protocol-defined treatment in the analysis at time *t*. Any deviations should be justified.

An overview of relevant ICEs should be reported and discussed to assess to what extent those ICEs could have impacted the PRO results. This may be supported by supplementary/ sensitivity analyses.

Explanation: if the PRO objective is confirmatory, it is important to preserve the ITT and safety population by collecting PROs after protocol deviation (as long as the patient remains on study) and to use this data in the analysis. Protocol deviations can be unavoidable events that may occur whilst treatments are compared. Therefore, PRO scores collected after the occurrence of such ICEs should be used in the main analysis, provided those deviations are not considered to impact the integrity of the clinical trial. When defining the estimand, the feasibility and usefulness (in light of the research objective) of collecting data after protocol

deviations should be taken into account. When such data is not collected, this should be justified. Sensitivity analyses may also be employed, where appropriate, to mitigate the effects of (partially) missing post-protocol deviation data.

An overview and reporting of relevant ICEs should help clarify to what extent those ICEs could have impacted the PRO results. Hence, reporting of ICEs is not requested for ICEs occurring after time *t* nor for ICEs that are not expected to change the observation or interpretation of the PRO endpoint of interest. If the PRO objective is limited to estimating while-on-treatment scores, then data collection can be stopped when protocol treatment discontinuation coincides with protocol deviation.

Example: the main goal is to compare specific PRO scores at month six between two treatment arms, but unauthorised concomitant rescue medication was administered to the patient at month four. The patient then continued protocol treatment and remained on study. PRO scores for that patient collected at month six must be used in the analysis regardless of the unauthorised concomitant rescue medication.

ICEprodev2_RCT

Statement: when the goal of the PRO objective is to draw conclusions about clinical benefit (confirmatory objective) using time-to-improvement within a time frame for a specific PRO domain: if a patient deviated from protocol-defined treatment before a PRO improvement occured (not causing treatment discontinuation), the main PRO analysis technique would be to use the PRO scores collected after deviation from protocol-defined treatment in the analysis to determine whether or not a PRO improvement occurred. Any deviations should be justified.

An overview of relevant ICEs should be reported and discussed to assess to what extent those ICEs could have impacted the PRO results. This may be supported by supplementary/ sensitivity analyses.

Explanation: if the PRO objective is confirmatory, it is important to preserve the ITT and safety population by collecting PROs after protocol deviation (as long as the patient remains on study) and to use this data in the analysis. Protocol deviations can be unavoidable events that may occur whilst treatments are compared. Therefore, PRO scores collected after the occurrence of such ICEs should be used in the main analysis, provided those deviations are not considered to impact the integrity of the clinical trial. When defining the estimand, the feasibility and usefulness (in light of the research objectives) of collecting data after protocol deviations should be taken into account. When such data is not collected, this should be justified. Sensitivity analyses may also be employed, where appropriate, to mitigate the effects of (partially) missing post-protocol-deviation data.

An overview and reporting of relevant ICEs should help clarify to what extent those ICEs could have impacted the PRO results. Hence, reporting of ICEs is not requested for ICEs occurring after the PRO improvement nor for ICEs that are not expected to change the observation or interpretation of the PRO endpoint of interest. If the PRO objective is limited to estimating while-on-treatment scores, then data collection can be stopped when protocol treatment discontinuation coincides with protocol deviation.

Example: the main goal is to compare time-to-improvement in a specific PRO domain between two treatment arms within a pre-specified time frame. The patient used unauthorised rescue medication before a PRO improvement was observed, and the patient remained in the study. PRO scores for that patient collected after unauthorised rescue medication administration must be used in the analysis regardless of this protocol deviation to determine whether a PRO improvement would be observed within the pre-specified time frame.

ICEprodev3_RCT

Statement: when the goal of the PRO objective is to draw conclusions about clinical benefit (confirmatory objective) using time-to-deterioration within a time frame for a specific PRO domain: if a patient deviated from protocol-defined treatment before a PRO deterioration occurred (not causing treatment discontinuation), the main PRO analysis technique would be to use the PRO scores collected after deviation from protocol-defined treatment in the analysis to determine whether or not a PRO deterioration occurred. Any deviations should be justified.

An overview of relevant ICEs should be reported and discussed to assess to what extent those ICEs could have impacted the PRO results. This may be supported by supplementary/ sensitivity analyses.

Explanation: if the PRO objective is confirmatory, it is important to preserve the ITT and safety population by collecting PROs after protocol deviation (as long as the patient remains on study) and to use this data in the analysis. Protocol deviations can be unavoidable events that may occur whilst treatments are compared. Therefore, PRO scores collected after the occurrence of such ICEs should be used in the main analysis, provided those deviations are not considered to impact the integrity of the clinical trial. When defining the estimand, the feasibility and usefulness (in light of the research objectives) of collecting data after protocol deviations should be taken into account. When such data is not collected, this should be justified. Sensitivity analyses may also be employed, where appropriate, to mitigate the effects of (partially) missing post-protocol-deviation data.

An overview and reporting of relevant ICEs should help clarify to what extent those ICEs could have impacted the PRO results. Hence, reporting of ICEs is not requested for ICEs occurring after the PRO deterioration event nor for ICEs that are not expected to change the observation or interpretation of the PRO endpoint of interest. If the PRO objective is limited to estimating while-on-treatment scores, then data collection can be stopped when protocol treatment discontinuation coincides with protocol deviation.

Example: the main goal is to compare time-to-deterioration in a specific PRO domain between two treatment arms within a pre-specified time frame. The patient used unauthorised rescue medication before a PRO deterioration event was observed and remained in the study. PRO scores for that patient collected after unauthorised rescue medication administration must be used in the analysis regardless of this protocol deviation to determine whether a PRO deterioration would be observed within the pre-specified time frame.

ICEprodev4_RCT

Statement: when the goal of the PRO objective is to draw conclusions about clinical benefit (confirmatory objective) using responder improvement at time *t* for a specific PRO domain: if a patient deviated from protocol-defined treatment before time *t* (not causing treatment discontinuation), the main PRO analysis technique would be to use the PRO scores collected after deviation from protocol-defined treatment in the analysis at time *t*. Any deviations should be justified.

An overview of relevant ICEs should be reported and discussed to assess to what extent those ICEs could have impacted the PRO results. This may be supported by supplementary/ sensitivity analyses.

Explanation: if the PRO objective is confirmatory, it is important to preserve the ITT and safety population by collecting PROs after protocol deviation (as long as the patient remains on study) and to use this data in the analysis. Protocol deviations can be unavoidable events that may occur whilst treatments are compared. Therefore, PRO scores collected after the occurrence of such ICEs should be used in the main analysis, provided those deviations are not considered to impact the integrity of the clinical trial. When defining the estimand, the feasibility and usefulness (in light of the research objectives) of collecting data after protocol deviations should be taken into account. When such data is not collected, this should be justified. Sensitivity analyses may also be employed, where appropriate, to mitigate the effects of (partially) missing post-protocol-deviation data.

An overview and reporting of relevant ICEs should help clarify to what extent those ICEs could have impacted the PRO results. Hence, reporting of ICEs is not requested for ICEs occurring after time *t* nor for ICEs that are not expected to change the observation or interpretation of the PRO endpoint of interest. If the PRO objective is limited to estimating while-on-treatment scores, then data collection can be stopped when protocol treatment discontinuation coincides with protocol deviation.

Example: the main goal is to compare the ratio of patients displaying improvement in PRO scores at month six for a specific domain (e.g. pain) between two treatment arms, but unauthorised concomitant rescue medication was administered to a patient at month four. PRO scores for that patient collected at month six must be used in the analysis regardless of the pain medication.

ICEprodev5_RCT

Statement: when the goal of the PRO objective is to draw conclusions about clinical benefit (confirmatory objective) using responder deterioration at time *t* for a specific PRO domain: if a patient deviated from protocol-defined treatment before time *t* (not causing treatment discontinuation), the main PRO analysis technique would be to use the PRO scores collected after deviation from protocol-defined treatment in the analysis at time *t*. Any deviations should be justified.

An overview of relevant ICEs should be reported and discussed to assess to what extent those ICEs could have impacted the PRO results. This may be supported by supplementary/ sensitivity analyses.

Explanation: if the PRO objective is confirmatory, it is important to preserve the ITT and safety population by collecting PROs after protocol deviation (as long as the patient remains on study) and using this data in the analysis. Protocol deviations can be unavoidable events that may occur whilst treatments are compared. Therefore, PRO scores collected after the occurrence of such ICEs should be used in the main analysis, provided those deviations are not considered to impact the integrity of the clinical trial. When defining the estimand, the feasibility and usefulness (in light of the research objectives) of collecting data after protocol deviations should be taken into account. When such data is not collected, this should be justified. Sensitivity analyses may also be employed, where appropriate, to mitigate the effects of (partially) missing post-protocol-deviation data.

An overview and reporting of relevant ICEs should help clarify to what extent those ICEs could have impacted the PRO results. Hence, reporting of ICEs is not requested for ICEs occurring after time *t* nor for ICEs that are not expected to change the observation or interpretation of the PRO endpoint of interest. If the PRO objective is limited to estimating while-on-treatment scores, then data collection can be stopped when protocol treatment discontinuation coincides with protocol deviation.

Example: the main goal is to compare the ratio of patients displaying deterioration in PRO scores at month six for a specific domain (e.g. pain) between two treatment arms, but unauthorised concomitant rescue medication was administered at month four to a patient; the patient continued protocol treatment and remained on study. PRO scores for that patient collected at month six must be used in the analysis regardless of the unauthorised concomitant rescue medication.

iii. Concomitant therapies allowed by the protocol

ICEconc1_RCT

Statement: when the goal of the PRO objective is to draw conclusions about clinical benefit (confirmatory objective) using magnitude of PRO (change) score at time *t* for a specific PRO domain: if a patient used concomitant therapies allowed by the protocol that could affect the interpretation of the PRO before time *t,* the main PRO analysis technique would be to use the PRO scores collected after patient started concomitant therapies in the analysis at time *t*. Any deviations should be justified.

An overview of relevant ICEs should be reported and discussed to assess to what extent those ICEs could have impacted the PRO results. This may be supported by supplementary/ sensitivity analyses.

Explanation: if the PRO objective is confirmatory, it is important to preserve the ITT and safety population by collecting PROs after the start of concomitant therapies (as long as the patient remains on study) and to use this data in the analysis. The start of concomitant therapies can be an unavoidable event that may occur whilst treatments are compared. Therefore, PRO scores collected after the occurrence of such ICEs should be used in the main analysis. When defining the estimand, the feasibility and usefulness (in light of the research objectives) of collecting data after the start of concomitant therapies should be taken into account. When such data is not collected, this should be justified. Sensitivity analyses may also be employed, where appropriate, to mitigate the effects of (partially) missing post-concomitant-therapy data.

An overview and reporting of relevant ICEs should help clarify to what extent those ICEs could have impacted the PRO results. Hence, reporting of ICEs is not requested for ICEs occurring after time *t* nor ICEs that are not expected to change the observation or interpretation of the PRO endpoint of interest. If the PRO objective is limited to estimating while-on-treatment scores, then data collection can be stopped when protocol treatment discontinuation coincides with the start of concomitant therapy.

Example: the main goal is to compare specific PRO scores at month six between two treatment arms. The patient was expected to complete PROs at month six but the patient used concomitant pain medications allowed by the protocol management plan at month five and remained on study. The primary PRO endpoint is pain. PRO scores for that patient collected at month six must be used in the analysis regardless of the pain medication.

ICEconc2_RCT

Statement: when the goal of the PRO objective is to draw conclusions about clinical benefit (confirmatory objective) using time-to-improvement within a time frame for a specific PRO domain: if a patient used concomitant therapies allowed by the protocol that could affect the interpretation of the PRO before a PRO improvement, the main PRO analysis technique would be to use the PRO scores collected after the patient started concomitant therapies to determine whether or not a PRO improvement occurred. Any deviations should be justified.

An overview of relevant ICEs should be reported and discussed to assess to what extent those ICEs could have impacted the PRO results. This may be supported by supplementary/sensitivity analyses.

Explanation: if the PRO objective is confirmatory, it is important to preserve the ITT and safety population by collecting PROs after the start of concomitant therapies (as long as the patient remains on study) and to use this data in the analysis. The start of concomitant therapies can be an unavoidable event that may occur whilst treatments are compared. Therefore, PRO scores collected after the occurrence of such ICEs should be used in the main analysis. When defining the estimand, the feasibility and usefulness (in light of the research objectives) of collecting data after the start of concomitant therapies should be taken into account. When such data is not collected, this should be justified. Sensitivity analyses may also be employed, where appropriate, to mitigate the effects of (partially) missing post-concomitant-therapy data.

An overview and reporting of relevant ICEs should help clarify to what extent those ICEs could have impacted the PRO results. Hence, reporting of ICEs is not requested for ICEs occurring after the PRO improvement nor for ICEs that are not expected to change the observation or interpretation of the PRO endpoint of interest.

If the PRO objective is limited to estimating while-on-treatment scores, then data collection can be stopped when protocol treatment discontinuation coincides with the start of concomitant therapy.

Example: the main goal is to compare time-to-improvement in a specific PRO domain between two treatment arms within a pre-specified time frame. The patient used pain relief medication before a PRO improvement was observed and they remained on study. PRO scores for that patient collected after the start of concomitant therapies allowed by the protocol must be used in the analysis to determine whether a PRO improvement would be observed within the pre-specified time frame.

ICEconc3_RCT

Statement: when the goal of the PRO objective is to draw conclusions about clinical benefit (confirmatory objective) using time-to-deterioration within a time frame for a specific PRO domain: if a patient used concomitant therapies allowed by the protocol that could affect the interpretation of the PRO before a PRO deterioration, the main PRO analysis technique would be to use the PRO scores collected after the patient started concomitant therapies to determine whether or not a PRO deterioration occurred. Any deviations should be justified.

An overview of relevant ICEs should be reported and discussed to assess to what extent those ICEs could have impacted the PRO results. This may be supported by supplementary/ sensitivity analyses.

Explanation: if the PRO objective is confirmatory, it is important to preserve the ITT and safety population by collecting PROs after the start of concomitant therapies (as long as the patient remains on study) and to use this data in the analysis. The start of concomitant therapies can be an unavoidable event that may occur whilst treatments are compared. Therefore, PRO scores collected after the occurrence of such ICEs should be used in the main analysis. When defining the estimand, the feasibility and usefulness (in light of the research objectives) of collecting data after the start of concomitant therapies should be taken into account. When such data is not collected, this should be justified. Sensitivity analyses may also be employed, where appropriate, to mitigate the effects of (partially) missing post-concomitant-therapy data.

An overview and reporting of relevant ICEs should help clarify to what extent those ICEs could have impacted the PRO results. Hence, reporting of ICEs is not requested for ICEs occurring after the PRO deterioration event nor for ICEs that are not expected to change the observation or interpretation of the PRO endpoint of interest.

If the PRO objective is limited to estimating while-on-treatment scores, then data collection can be stopped when protocol treatment discontinuation coincides with the start of concomitant therapy.

Example: the main goal is to compare time-to-deterioration in a specific PRO domain between two treatment arms within a pre-specified time frame. The patient used pain relief medication before a PRO deterioration event was observed and remained on study. PRO scores for that patient collected after the use of concomitant therapies allowed by the protocol must be used in the analysis to determine whether a PRO deterioration would be observed within the pre-specified time frame.

ICEconc4_RCT

Statement: when the goal of the PRO objective is to draw conclusions about clinical benefit (confirmatory objective) using responder improvement at time *t* for a specific PRO domain: if a patient used concomitant therapies allowed by the protocol that could affect the interpretation of the PRO before time *t*, the main PRO analysis technique would be to use the PRO scores collected after patient started concomitant therapies in the analysis at time *t*. Any deviations should be justified.

An overview of relevant ICEs should be reported and discussed to assess to what extent those ICEs could have impacted the PRO results. This may be supported by supplementary/sensitivity analyses.

Explanation: if the PRO objective is confirmatory, it is important to preserve the ITT and safety population by collecting PROs after the start of concomitant therapies (as long as the patient remains on study) and to use this data in the analysis. The start of concomitant therapies is an unavoidable event that may occur whilst treatments are compared. Therefore, PRO scores collected after the occurrence of such ICEs should be used in the main analysis. When defining the estimand, the feasibility and usefulness (in light of the research objectives) of collecting data after the start of concomitant therapies should be taken into account. When such data is not collected, this should be justified. Sensitivity analyses may also be employed, where appropriate, to mitigate the effects of (partially) missing post-concomitant-therapy data.

An overview and reporting of relevant ICEs should help clarify to what extent those ICEs could have impacted the PRO results. Hence, reporting of ICEs is not requested for ICEs occurring after time *t* nor for ICEs that are not expected to change the observation or interpretation of the PRO endpoint of interest.

If the PRO objective is limited to estimating while-on-treatment scores, then data collection can be stopped when protocol treatment discontinuation coincides with the start of concomitant therapy.

Example: the main goal is to compare the ratio of patients displaying improvement in PRO scores at month six for a specific domain (e.g. pain) between two treatment arms, but a patient used concomitant pain medications allowed by the protocol management plan at month five. PRO scores for that patient collected at month six must be used in the analysis regardless of the pain medication.

ICEconc5_RCT

Statement: when the goal of the PRO objective is to draw conclusions about clinical benefit (confirmatory objective) using responder deterioration at time *t* for a specific PRO domain: if a patient used concomitant therapies allowed by the protocol that could affect the interpretation of the PRO before time *t*, the main PRO analysis technique would be to use the PRO scores collected after patient started concomitant therapies in the analysis at time *t*. Any deviations should be justified.

An overview of relevant ICEs should be reported and discussed to assess to what extent those ICEs could have impacted the PRO results. This may be supported by supplementary/ sensitivity analyses.

Explanation: if the PRO objective is confirmatory, it is important to preserve the ITT and safety population by collecting PROs after the start of concomitant therapies (as long as the patient remains on study) and to use this data in the analysis. The start of concomitant therapies can be an unavoidable event that may occur whilst treatments are compared. Therefore, PRO scores collected after the occurrence of such ICEs should be used in the main analysis. When defining the estimand, the feasibility and usefulness (in light of the research objectives) of collecting data after the start of concomitant therapies should be taken into account. When such data is not collected, this should be justified. Sensitivity analyses may also be employed, where appropriate, to mitigate the effects of (partially) missing post-concomitant-therapy data.

An overview and reporting of relevant ICEs should help clarify to what extent those ICEs could have impacted the PRO results. Hence, reporting of ICEs is not requested for ICEs occurring after time *t* nor for ICEs that are not expected to change the observation or interpretation of the PRO endpoint of interest.

If the PRO objective is limited to estimating while-on-treatment scores, then data collection can be stopped when protocol treatment discontinuation coincides with the start of concomitant therapy.

Example: the main goal is to compare the ratio of patients displaying deterioration in PRO scores at month six for a specific domain (e.g. pain) between two treatment arms, but a patient used concomitant pain medications allowed by the protocol management plan at month five and remained on study. PRO scores for that patient collected at month six must be used in the analysis regardless of the pain medication.