EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

26 September 2023

The International Society for CNS Clinical Trials and Methodology, ISCTM, welcomes the opportunity to provide comment on the "Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation" drafted by the European Medicines Agency.

The ISCTM was chartered in the fall of 2004 as an international society charged with providing a commercial free forum where key stakeholders from academia, industry and regulatory branches can discuss/resolve challenges specific to the design and methodological issues in CNS clinical trials. Recognizing the importance of this document for our constituency, the ISCTM convened a working group to review and comment on the paper.

For this response, the group has provided some recommendations regarding the agency's proposal on establishing efficacy based on single-arm trials.

Below please find contributors to the ISCTM working group on "Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation."

Co-chair: Atul Mahableshwarkar, MD, Independent
Co-chair: Siân Ratcliffe, PhD, Biogen
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Submission of comments on 'Reflection paper on establishing efficacy based on single-arm trials submitted

as pivotal evidence in a marketing authorisation' (EMA/CHMP/564424/2021)

Comments from:

Name of organisation or individual
ISCTM

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	ISCTM welcomes EMA sharing their current thinking on single arm trials as pivotal evidence in marketing authorisations. The draft reflection paper is a very important and helpful document to guide decisions on what constitutes an appropriate trial design, for example in the rare disease space. As a group focused on CNS clinical trial methodology, ISCTM would welcome more references to examples where single arm trials could be applied, eg in rare/ultra-rare diseases, pediatrics and other therapeutic areas, including neuroscience. In addition to specific comments in Section 2 below, ISCTM has some general comments of note: 1) It would be helpful if this reflection paper also addressed methodological and statistical aspects such as contemporaneous or external controls or use of Bayesian dynamic borrowing. 2) This reflection paper focuses on endpoints related to efficacy, it would be helpful to also address biomarker and PRO endpoints, given the value that these might have in building the totality of evidence in support of an investigational drug.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Lines 27-28		Comment: Adding this will support the statement with data and inform the field Proposed change (if any): However, in a relevant proportion of marketing authorisation applications the pivotal clinical data stems from single-arm trials (SATs) e.g. please provide examples	
Lines 40-43		Comment: Appropriately evaluating safety needs larger Ns than establishing efficacy and outlining agency's thinking on that will strengthen this document Proposed change (if any): Suggest adding a short explanation regarding establishment of safety.	
Line 58		Comment: This would more clearly differentiate screened vs. enrolled vs. participants as including ineligible patients who screen failure would not provide appropriate data Proposed change (if any): all subjects who are enrolled in the trial and deemed to be eligible and receive treatment	
Line 73		Comment: Increasing clarity and internal consistency of the text	

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		Proposed change (if any): External information to the SAT	
Line 104		Comment : Consider to add the definition of Real World Data. Proposed change (if any):	
Line 126-127		Comment: Reinforce the need to carefully control timing/tracking of treatment initiation. i.e., provide actionable steps Proposed change (if any): In SAT's even the timing of treatment initiation may be less clear than in RCTs. Given the nature of SATs, i.e., with no control group to compare to, it would be beneficial to ensure careful control over treatment initiation timing.	
Lines 72-73 and 140-146		Comment: The text in lines 140-146 "Conceptually, this can allow a causal interpretation of the effect of the treatment, despite the limitations in study design." Appears to contradict the text in lines 72-32 "Due to the lack of randomisation, the design does not support a causal interpretation as an effect of the treatment" The meaning of the text should be clarified. Proposed change (if any)	
Lines 141-142		Comment: Be more explicit in stating that methodologies need to be assessed on a case-by-case basis (might be redundant text suggestion) Proposed change (if any): There is no general statistical or	

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		methodological definition for the concept of isolating a treatment effect, and so justification of methods factoring in trial circumstances is necessary.	
Lines 148-150		Comment: Examples of "exceptional cases" which will fully satisfy the certainty of causal relation between the treatment and outcome as measured by the endpoint should be provided/included to increase the clarity of the text. Proposed change (if any): Specifically, there must be qualitative reasoning that leaves no doubt about the causal relationship between the treatment and outcome measured by the endpoint; which will only be fully satisfied in exceptional cases such as-please provide some examples to help guide the field	
Line 150		Comment: Improve ease of reading. It is reasonably implied that sources of variability can be various if unspecified Proposed change (if any): In practice, observed individual outcomes are subject to bias and ~~various sources of~~ variability	
Line 151		Comment: Avoid the implication that RCTs can be subject to bias due to measurement errors, but that SATs are not as subject to bias due to measurement errors and are more sensitive due to the lack of a concurrent control group Proposed change (if any): Hence, even more so than in ~~contrast to~~ RCTs, measurement errors	

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Line 168		Comment: Sentence appears to have some words missing Proposed change (if any): …may be equally prone to error due to the selection of patients…	
Line 181		Comment: The way it was written made an implicit linkage between bias and differences between estimate/population effects. Although this is valid, it would improve ease of reading to make this explicit Proposed change (if any): …and the true treatment effect in the target population. The bias induced by differences between the trial arm response and the true population response also applies to treatment effect estimates from RCTs if the treatment effect differs between subgroups and the trial population is not representative of the target population.	
Lines 204-205		Comment: Suggest providing some examples (from more than one therapeutic area) of situations in which evidence from SATs may be considered. Providing such examples will help the field understand when SATs may be considered by sponsors to establish efficacy for marketing authorization applications. Proposed change (if any): However, in certain situations, (for example…please provide some examples) evidence from SATs may	

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Line 208		Comment: add another type of endpoints such as Ordinal endpoints, Lickert Scales. This is relevant because Global Impression Scales use this type of measure and are also used as anchors to validate other endpoints. Including this type of ordinal endpoints, this will cover CGI, PGI and Caregiver GI. Proposed change (if any)	
Line 230		Comment: The clinical management of a condition might vary from country to country, hence it would be useful to have representativity including clinicians from different parts in EU. Proposed change (if any): Whether or not a specific endpoint is acceptable in a therapeutic area or allows establishing of a clinically relevant treatment effect needs to be discussed on clinical grounds as clinical management of a condition might be different in different countries.	
Lines 239-240		Comment: While the current wording relates to analyses from Time 0, with a well-established natural history (such as mortality in the natural history of SMA Type 1), the statement as currently written may imply age-dependent analyses would not be appropriate Proposed change (if any): Exceptions could be endpoints that measure time to positive events or events (such as mortality in SMA Type 1) based on age and established from the natural history of the disease that cannot occur without treatment	

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Line 271		Comment: A binary endpoint may also be appropriate (such as mortality) based on age. This further differentiates analyses from Time 0 and allowance for age-based analyses Proposed change (if any): This can also apply to cases where patients are alive at a time point or age that substantially exceeds	
Line 308-310		Comment: Having these details would provide support to the position that the trial population is a representative sample of the condition being studies Proposed change (if any): In addition to well justified inclusion and exclusion criteria this includes details about the screening process, clinical characteristics of the subjects, the decision for trial inclusion, and about the subjects who were not selected.	
Line 324		Comment: Narrative continuity with this section Proposed change (if any): …within the targeted biomarker-defined subgroup…	
Lines 179-193 and Line 330		Comment: This is where biomarkers are presented in the document. However, in the paragraph on external validity (lines 179-193) it is stated that the role of biomarkers could bias the results of SATs. Can this be aligned or explained?	

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		Proposed change (if any)	
Line 336		Comment: To increase clarity and internal consistency of the text Proposed change (if any): external ~~(extra-study)~~ extra-study information	
Line 352		Comment: To increase clarity and internal consistency of the text Proposed change (if any): (i.e. ~~an~~ external control group data)	
Line 353		Comment: To increase clarity and internal consistency of the text Proposed change (if any): external clinical data is beyond the scope of this reflection paper.	
Line 354		Comment: To increase clarity and internal consistency of the text Proposed change (if any): external clinical data into the analysis come with a promise to provide	
Lines 377-378		Comment: As written - this could imply that interim assessments of unblinded data would be disallowed. These types of informal assessments of an ongoing trial may be important to assess potential risk:benefit ratio to the patient of an ongoing disease	

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		Proposed change (if any): This includes unplanned interim analyses (i.e., formal statistical comparisons that would impact alpha for multiple comparisons), changes in endpoints, changes in or deviations from the planned number of patients (sample size re-estimation)	
Line 391		Comment: To increase clarity of the text Proposed change (if any): ~~(randomised)~~ randomised clinical trials apply also for SATs	
Lines 394-397		Comment: Text in the document states, "Predefinition of the primary analysis set is of utmost importance and bias due to inclusion or exclusion of patients in the analysis set based on observed individual outcomes should be avoided. Therefore, the full analysis set, i.e. all subjects that entered the SAT upon providing informed consent, should be used as the primary analysis set." Should this reflect the ITT population in a RCT? There are in/exclusion criteria to be assessed also for a SAT that could result in screen failure, e.g. conditions that would prevent safe administration of IMP. As stated previously, these should be reported, but should be excluded from the full analysis set in my view/definition. Proposed change (if any)	

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Line 396		Comment: As written - this would include patients who are screened for a study, but does not account for the potential that screened patients are ineligible for treatment and fail screening Proposed change (if any): i.e., all subjects that entered the SAT upon providing informed consent and receive treatment, should be used as the primary analysis set	
Line 415		Comment: Account for data missingness types Proposed change (if any): …do not overestimate the response to treatment, and additionally account for potential types of missingness in the data.	
Line 423-425		Comment: Add text to highlight need for method justification, remove over-specific comment on non-/parametric stats methods Proposed change (if any): All analyses should be pre-defined in a detailed statistical analysis plan (that includes justification of chosen statistical methods) before the SAT starts, i.e. before inclusion of the first patient. ~~For the statistical analysis of a SAT, applicable non-parametric or 425 parametric statistical methods may be applied.~~	
Line 430		Comment: To increase clarity of the text	

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		Proposed change calibrated against a control that shares the same (if any) randomised characteristics.	
Line 457-458		Comment: Please further specify the terminology "negligible extent" to clarify text. Proposed change (if any)	
Line 471-475		Comment: Using the lower or upper limit of 95%CI appears to be a conservative approach, and if the test value and CIs is below the lower or above the upper limit of the standard CI it should be sufficiently different. Case-by-case one could discuss this, but not accepting this seems to be too conservative. Proposed change (if any)	
Line 473		Comment: To increase clarity and internal consistency of the text Proposed change (if any): instead of the point estimate as derived based on external clinical data	
Line 493		Comment: Comment: To increase clarity of the text Proposed change (if any): some of which also apply to open label ~~(open label)~~ RCTs	
Line 498 Table 1		Comment: From Row 2 Column 3 Term "objective" is ambiguous and should be clearly specified. Is the text specifically referring to endpoints based on instrumental "machine" methods (i.e., Imaging, Labs, EKG, etc.) then	

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		excluding Clinician Judgment, Study Participant's performance, and Patient Reported Outcomes? Alternatively, is the text referring to properties of reliability and validity of measurements to be applied? Proposed change (if any)	
Line 498 Table 1		Comment: Suggest text be modified, the term "independently" should be better clarified/defined. As an Investigator who I am supposed to be dependent upon when assessing clinical data? As Investigator, how can I assess patient's safety If I'm not aware of timing in relation to treatment? This sentence may be incorrectly perceived as putting study participant's safety "on a back seat". Proposed change (if any)	
Line 498 Table 1		Comment: From Row 3 Column 2 in Table: Actually attrition patients and missing data of study participants and missing data refer to two different sources of bias. The risk mitigating strategy refers to missing data only. Proposed change (if any): ~~Attrition of patients and~~ Missing data in general constitute an additional source of confounding that is difficult to resolve.	
Line 498 Table 1		Comment: From Row 8 column 2 To increase clarity and internal consistency of the text	

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		Proposed change (if any): external clinical data	
Line 498 Table 1		Comment: From Row 8 column 3 To increase clarity and internal consistency of the text Proposed change (if any): The start time of being at risk (time 0) needs to be clearly defined, should time to-event endpoints including a comparison to external data be required; the data set needs to as complete as possible to avoid bias due to missing data	
Line 498 Table 1		Comment: From Row 11 Column 2 Suggest text be clarified as to whether it is referring to patient's medical history or disease history (i.e., characteristics of disease evolution over time, course of the disease targeted for treatment) Proposed change (if any) Patients enrolled in a SAT may systematically differ from the hypothetical control group in ways that impact their prognosis. Please clarify if the systematic differences are referring to patients disease being studied or other medical conditions that may impact their prognosis.	
Line 498 Table 1		Comment: From Row 8 Column 2 Advise to remove "previous studies" as redundant to increase clarity of the text Proposed change (if any): Study or treatment start relative to ~~previous studies or~~ external clinical data is difficult to determine as an anchor for patient specific time scale.	

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		Comment: Proposed change (if any)	

Please add more rows if needed.