07 February 2025

Medicines and Healthcare products Regulatory Agency (MHRA)
10 South Colonnade
Canary Wharf
London
E14 4PU
via online submission to MHRA

RE: MHRA Consultation on the International Council for Harmonisation (ICH) E6(R3) Good Clinical Practice (GCP) Annex 2 *Respondent ID: 7e0f5497-2876-4229-acba-d78916588524*

Dear Sir or Madam,

The International Society for Pharmaceutical Engineering (ISPE) appreciates the opportunity to comment on Annex 2 of the International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) Guideline.

ISPE members appreciate the MHRAs efforts to support the ICH Guideline.The Guideline effectively includes Real-World Data (RWD) in clinical trials. It emphasizes retaining essential records from decentralized clinical trials (DCT), digital health technologies (DHT), and RWD, ensuring data remains accessible and not locked in proprietary formats but should provide strategies to ensure data reliability and regulatory relevance. The guideline positively acknowledges remote consent but should specify validated identity verification methods to support diverse populations. A common data standard across RWD, digital twin, and AI sources is recommended, as guidance on digital twin and AI is currently limited.

Training for investigators, site staff, and participants could be expanded to include specific guidance on advanced technology use. Standardizing data formats and harmonizing terminologies across different sources is crucial for consistency and reliability in clinical trials.

ISPE is a not-for-profit organization of individual members from pharmaceutical companies, contract manufacturing organizations, suppliers and service providers, and health authorities. ISPE's 22,000+ members lead scientific, technical, and regulatory advancement throughout the entire pharmaceutical lifecycle in more than 90 countries around the world. ISPE does not take a political position or engage in lobbying activities or legislative agendas.

We appreciate the opportunity to submit these comments for your consideration. Please do not hesitate to contact me if you have any questions.

Respectfully,

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cc: Jeff Biskup, ISPE Chairman

Response for comments: **Consultation on the International Council for Harmonisation ICH E6 (R3) Guideline for Good Clinical Practice Annex-2**

Comments submitted by the International Society for Pharmaceutical Engineering (ISPE), regulatorycomments@ispe.org

GENERAL COMMENTS ON THE DOCUMENT
ICH GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R3) Annex 2 appropriately addresses the inclusion of Real-World Data (RWD) in clinical trials but would benefit from recommending strategies to ensure the reliability and relevance of the data for use in a regulatory context. The document should reinforce the requirements for retaining essential records, originating from DCT/DHT/RWD, including that data should remain readable and usable. These should be considered in the design and protocol of a trial, for example ensuring that source data is not left in proprietary formats and locked into proprietary devices, for example wearables or instruments. Successful long-term data retention is best achieved by design from the outset as part of data collection, rather than considered as an afterthought when a study is completed.
The inclusion of remote consent modalities is a positive development. However, it is recommended to specify validated methods for identity verification and ensure that the process is understandable and usable for diverse populations, particularly those with limited technological familiarity or access to digital tools.
ISPE Members suggest the Annex recommends the use of a common standard across data sources not just with RWD but also including other technological advances such as digital twin, AI and data from these sources. There is an increased use of digital twin and AI in clinical trials but Annex 2 contains limited guidance on these.
The need for training for investigators, site staff, and participants is briefly mentioned. Given the use of advanced technologies, it would be helpful to include specific guidance on training programs and support materials to facilitate the proper implementation and use of digital devices, thereby improving data quality, data management and protocol adherence.
Data from different sources may use varying terminologies and standards, leading to potential inconsistencies. This can involve mapping different terminologies to a common standard, using standardized data models, and employing data harmonization techniques. Ensuring that data from different sources can be accurately compared and integrated is essential for the validity of the clinical trial results. Standardizing data formats is crucial for ensuring comparability and reliability and needs clarification

The document does not include any guidance on the potential need for validation of Digital Health Technologies (DHT)s. This may be covered in other areas of ICH E6 R3
The structure of the document could be improved by having dedicated sections for DHT and RWD. This may lead to some repetition but would improve readability of the overall document.

Specific Comments on the Text

ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
39 - 43	"The ethical principles and standards for the evaluation of clinical trials by IRBs/IECs as described in the Principles and Annex 1, provide a sound basis for the conduct of clinical trials, including those incorporating decentralised elements, pragmatic elements and/or RWD. Particular attention should be given, for example, to privacy and confidentiality of the participants and security of their data."	Suggest additional sentence: **IRB and IECs should have a technology expert present when making ethical decisions to ensure that the platforms, technologies and evidence provided are truly understood.**	No mention is given to ensure that IRBs and IEC have a sound knowledge of the technology platforms used and that the data collection using those are ethical.
56 - 58	"Informed consent may be obtained remotely, where appropriate. When informed consent is obtained remotely, the investigator should assure themselves of the identity of the participant (or legally acceptable representative where applicable) in	Informed consent may be obtained remotely, where appropriate **using secure digital tools or real-time verification. The investigator should document the informed consent and should obtain the signature of the participant or legal representative, where applicable, either via**	Remote consent introduces risks of identity fraud and non-compliance. Specifying secure methods ensures robust identity verification and maintains the validity of the consent process. This is consistent with ICH E6(R3) Annex 1, Section 2.8, ensuring security and validity in the informed consent process.

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	accordance with applicable regulatory requirements."	**electronic means or paper-based,** When informed consent is obtained remotely, the investigator should assure themselves of the identity of the participant (or legally acceptable representative where applicable) in accordance with applicable regulatory requirements.	Informed consent should be signed, unless there is a valid reason where signatures can be waived under applicable regulatory requirements. Verbal, Electronic and Implied Consent may be utilized. There is still a requirement to document the informed consent – that the investigator or a study representative has explained the required information to the participant either verbally or in written form.
83 - 84	"When shipping investigational products to a participant, the following should be considered..."	Suggest adding an additional sub-bullet: **(f) Sponsors should assess the need for monitoring tools, such as temperature sensors, to ensure required storage conditions are maintained during shipping.**	Maintaining investigational product integrity during shipping is critical for trial outcomes and participant safety. Including monitoring tools, such as temperature sensors, ensures compliance with product storage requirements and reduces risks associated with improper handling. This aligns with ICH E6(R3) Annex 1, Section 3.15.3 (Product Accountability).
85 - 86	"The process for protecting the privacy and maintaining the confidentiality of the participant and their disease status."	The process for protecting the privacy and maintaining the confidentiality of the participant'**s personal information and disease status for all except Investigator designated parties**.	This is an investigator responsibility but direct to patient services are often organized by the sponsor. ISPE suggests clearer text that participant confidentiality includes confidentiality towards the sponsor.
89 - 90	"The process for the receipt, storage, handling, administration, return, destruction or alternative disposition	The process for the receipt, storage, **product and data** handling, administration, return, destruction or alternative disposition and	Often there are problems experienced with the participant's handling of temperature loggers and their data. A

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	and accountability of the investigational product."	accountability of the investigational product.	process should describe who and how this data needs to be handled.
92 - 93	None	Suggest adding an additional sub-bullet: **(g) The process for training participants facing providers in responding to participant questions.**	Often participants address questions (e.g. AE related) to couriers who have no healthcare or trial training. At the minimum they should be instructed to refer the patient to a designated content for those questions.
101	"See section ~~2.3~~ on the level of oversight. "	See section **2.4** on the level of oversight.	Error in section number for Investigator Oversight section.
107 - 108	(b) "Commencement, continuation, dose and dose adjustments of the allocated investigational product in accordance with the protocol."	Commencement, continuation, dose and dose adjustments of the allocated investigational product, **and reflecting the participant's adherence to the investigational product's dosing regimen**, in accordance with the protocol.	Since there may be less oversight on treatment adherence to the dosing regimen at the patient home, it is recommended to call this out more explicitly.
109	"2.4 Investigator Oversight"	Investigator Oversight **of Trial-Related Activities**	The entire section 2 is about the Investigator, and the oversight the investigator should maintain. Section 2.4 is specially referring to the oversight of HCPs conducting trial-related activities, so the current title does not reflect the sub-section.
141 - 144	"This engagement may bring attention to areas where additional training or support may be needed (e.g., digital literacy, physical ability or lack of access to technology that may require the use of alternative approaches,	This engagement may bring attention to areas where additional training or support may be needed (e.g. digital literacy, physical ~~ability~~ **limitations** or lack of access to technology that may require the use of alternative	Physical "limitations" would expand the scope to include the ability to use the technology or allergic reactions to materials used in wearables such that

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	specialized training or the provision of technology)."	approaches, specialized training or the provision of technology).	an alternative material may be offered/considered for participants.
165 - 166	"The specific design elements and data sources should be adequately described in the protocol, and the appropriateness of their use justified."	The specific design elements, data sources **and the data flow** should be adequately described in the protocol, and the appropriateness of their use justified.	It is important that the flow of data between Sites, Patients (in case DHTs or other decentralized elements) and sponsors across the various systems is documented to enable appropriate oversight by the investigator and/or the sponsor.
170 - 172	"Since data may originate from different sources or various practice settings (e.g., sources with different timing of data collection), there may be data variability within and/or between data sources/settings."	Suggest adding that the protocol could also address potential limitations or biases associated with the data sources or collection methods and describe strategies to mitigate those limitations. Especially factors like how recent the data is and what time frame does it cover, the representativeness of the data in terms of demographics geographic coverage etc. and amount of patient records included in the data should be included in the assessment of data sources to avoid potential bias.	Some guidance regarding Bias (and how to avoid it) should be included (preferably as a separate point). Factors such as limited data from specific provider systems, demographic or socioeconomic biases and selection biases based on physician preferences or utilization patterns can affect the representativeness of the data. Additionally, EHRs may contain systematic biases related to billing practices such as down or up coding. Alternatively, this can be added to Section 3.5.1
175 - 177	"The design elements and data sources should be considered when determining the need for appropriate training and technical support to be provided to the investigator,	The design elements and data sources should be considered when determining the need for appropriate training and technical support to be provided to the investigator, investigator site staff and participants (see Annex 1, section 2.3.2). **The protocol should detail training**	Decentralized trials rely on advanced technologies, which require proper training for investigators and participants. Including this detail ensures that all stakeholders understand and effectively use tools like wearables or remote monitoring systems, reducing errors and improving

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	investigator site staff and participants (see Annex 1, section 2.3.2)."	**programs for both investigators and participants to ensure the correct use of the digital tools.**	trial data quality. This aligns with ICH E6(R3) Annex 1, Section 2.3.2, which highlights the importance of training to ensure reliable data collection and protocol adherence.
194 - 196	"In situations where RWD are used, the sponsor should ensure that ~~appropriate consent or permission for the use of the data~~ has been obtained in accordance with applicable regulatory requirements."	In situations where RWD are used, the sponsor should ensure that **detailed consent, specifying the use of each type of RWD,** has been obtained in accordance with applicable regulatory requirements."	The current text does not specify how consent should be tailored to different types of RWD, particularly for retrospective data. Providing more specific guidance ensures compliance with regulations and participant understanding, particularly in cases where data is reused from external sources like EHRs or registries. This aligns with GDPR (where applicable), which emphasizes the importance of specific, detailed consent for secondary use of data. It also addresses ethical considerations in ICH E6(R3) Annex 1, Section 2.8 (Informed Consent).
200	Section 3.5.1	An additional point under 3.5.1 could be: **The protocol should consider the essential records and the requirements for Record Keeping and Retention including the approach to data collection, data formats, and data management. Consideration should be given to how data is captured, transferred, migrated and retained in a way that**	Data integrity and retention concerns.

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		ensures data remains complete, integral, readable and readily available throughout the full data lifecycle.	
207 - 208	"The potential variability of data formats (e.g., different terminologies and/or standards) with data coming from a variety of sources."	The potential variability of data formats (e.g., different terminologies and/or standards) with data coming from a variety of sources **should be addressed by a harmonization strategy before integration**.	Variability in data formats and collection timing can introduce inconsistencies that compromise data reliability. Recommending a harmonization strategy explicitly ensures better alignment of data from diverse sources, improving the quality and integrity of clinical trial results. This aligns with ICH E8(R1), which emphasizes fitness for purpose in data quality.
214 - 220	"Missing data (e.g., due to participants moving to different healthcare systems) or the occurrence of intercurrent events between clinical visits that may be difficult to capture or ascertain when using RWD (e.g., discontinuation of treatment or the use of an additional or alternative therapy that is not captured in the EHR). See ICH E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on 219 Statistical Principles for Clinical Trials."	Missing data (e.g., due to participants moving to different healthcare systems) or the occurrence of intercurrent events between clinical visits that may be difficult to capture or ascertain when using RWD (e.g., discontinuation of treatment or the use of an additional or alternative therapy that is not captured in the EHR). **Furthermore, duplicate values, redundant data points or observations reported multiple times as well as outliers may need to be considered.** See ICH E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to	Added additional factors that might need to be considered in the usage of RWD.

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		the Guideline on Statistical Principles for Clinical Trials.	
221 - 223	"The overall quality of data collected in clinical practice (e.g., EHR, claims data) or registries, including operational processes and database structure, consistency of vocabularies and coding systems."	The overall quality of data **used in support of a clinical trial including that** collected in clinical practice (e.g., EHR, claims data) or registries, including operational processes and database structure, consistency of vocabularies and coding systems.	Data quality needs to be fundamental to all data used in support of a clinical trial.
226 - 227	"The validation status of tools used for the acquisition of RWD (e.g., registries), as appropriate."	Please clarify the expectations for validation of systems used for the acquisition of RWD	If the expectation is that all RWD systems are validated, this may lead to very little acceptable sources of RWD.
235 - 238	"In such cases, the sponsor should have agreements with those entities in place that allow regulatory authorities to access the source records and data for the purpose of conducting regulatory inspections in accordance with applicable regulatory requirements. "	In such cases, the sponsor should have agreements with those entities in place that allow regulatory authorities to access the source records and data for the purpose of conducting regulatory inspections **throughout the entire retention period** in accordance with applicable regulatory requirements.	Added the retention period as a critical factor.
247 - 251	"Remote data collection in clinical trials that incorporate decentralised and pragmatic elements (e.g., the use of remote visits and DHTs, such as wearables, or the extraction of data from EHRs) requires special attention to be paid to data security vulnerabilities (see Annex 1, section	Remote data collection in clinical trials that incorporate decentralised and pragmatic elements (e.g., the use of remote visits and DHTs, such as wearables, or the extraction of data from EHRs) requires special attention to be paid to data security vulnerabilities (see Annex 1, section	Processes for DHTs are vital to ensure security, privacy and integrity of data.

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	4.3.3), including cybersecurity and data privacy (see section 3.7)."	4.3.3), including cybersecurity and data privacy (see section 3.7). **For DHTs, appropriate processes need to be in place for provisioning, management (including potential replacement), maintenance and decommissioning of such technologies.**	
252 - 253	(b) Some of the RWD considerations in section 3.5.1 may also apply to remote clinical trial data collection (e.g., DHTs including wearables).	(b) ~~Some of the~~ RWD Considerations in section 3.5.1 ~~may~~ also apply to remote clinical trial collection (e.g. DHT's including wearables). **Additional considerations may include but are not limited to:** **(i) Calibration and validation of the DHT's used to collect data remotely (e.g. data collected by wearables should conform to a pre-set standard, where applicable).** **(ii) Integrity of the data collected using DHT's (e.g. data should be attributable to the participant).**	Although the statement is accurate, it is very high level. Specific considerations should be added.
273 - 276	"The sponsor may deploy systems (e.g., interactive response technology, DHTs) and assist the investigator to establish processes (e.g., home nurse visits) to ensure that the allocated	The sponsor may deploy systems (e.g., interactive response technology, DHTs) and assist the investigator to establish processes (e.g., home nurse visits) to ensure that the allocated investigational product **and/or DHT**	Adjusted wording.

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	investigational product was delivered and administered appropriately to the trial participant."	was delivered and administered appropriately to the trial participant.	
277 - 286	"Sponsors should ensure security safeguards, including cybersecurity, are in place to protect the privacy and confidentiality of personal information of trial participants. Participants' personal information may be required by service providers to fulfil their activities (e.g., disclosure of personal information when investigational product is shipped to participants or when a home nurse is deployed, where appropriate). In these circumstances sponsors and service providers should ensure that appropriate informed consent has been provided by the participant, that the personal information is protected from inadvertent disclosure and that access to these data is limited to those authorised. The sponsors should address the risk of potential disclosure of personal information from a data breach when data from DHTs and/or RWD are used."	Sponsors should ensure security safeguards, including cybersecurity, are in place to protect the privacy and confidentiality of personal information of trial participants. Participants' personal information may be required by service providers to fulfil their activities (e.g., disclosure of personal information when investigational product is shipped to participants or when a home nurse is deployed, where appropriate). In these circumstances sponsors and service providers should ensure that appropriate informed consent has been provided by the participant, that the personal information is protected from inadvertent disclosure and that access to these data is limited to those authorised. The sponsors should address the risk of potential disclosure of personal information from a data breach when data from DHTs and/or RWD are used **and develop and maintain an incident response plan accordingly.**	While cybersecurity measures are mentioned, there is no guidance on managing breaches. An incident response plan ensures rapid mitigation of data breaches, protecting participant confidentiality and upholding regulatory compliance. ICH E6(R3) Annex 2, Section 3.7, requires robust privacy safeguards, but including those details, it will help to be aligned with global data protection regulations like GDPR and local cybersecurity laws.
302 - 304	"The safety information should be provided in an actionable manner that provides the investigator with an	The safety information should be provided in an actionable manner that provides the investigator with an	Decentralized trials often generate safety data from diverse sources, leading to potential delays in identifying

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	overview on the health status of the trial participant.”	overview on the health status of the trial participant. **Sponsors should seek to establish automated systems to integrate and prioritize safety signals from multiple data sources in real time.**	risks. Automated systems enable timely integration and prioritization of safety signals, ensuring prompt investigator action and improved participant safety. This aligns with ICH E6(R3) Annex 1, Section 2.7 (Participant Safety).

End of comments