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Frequently Asked Questions

The following are questions about annotated ECG waveforms supporting ICH E14 QT assessment typically reviewed by CDER Interdisciplinary Review Team for Cardiac Safety Studies (formerly QT-IRT). Please visit IRT's web[1] for more information about cardiac safety studies.

[1] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt

1 Submitting ECG waveform data

1.1 Should the annotated ECG waveforms be submitted to ecgwarehouse.com, FDA Electronic Submissions Gateway (ESG) or both?

Digital ECG waveforms with annotations in electronic format (XML) following the HL7 annotated ECG (aECG) standard should be submitted to the FDA Electronic Submissions Gateway (ESG). The former ecgwarehouse.com is no longer accepting uploads (FAQ 1.2)

1.2 Is it still possible to upload waveforms to ecgwarehouse.com?

No. Since April 2021, ecgwarehouse.com is no longer accepting uploads.

1.3 What is the recommended folder in the eCTD structure for placing annotated ECG waveform files?

When submitting through the ESG, we recommend placing the ECGs in an *aecg* folder under the *misc* folder (e.g., m5 -> datasets -> [study-id] -> misc -> aecg).

1.4 Is it possible to submit ECG waveforms without annotations?

It is recommended to include annotations when submitting ECG waveforms supporting ICH E14 QT assessment. The annotations in the ECG waveforms are used to evaluate QT measurement bias and allow for cross-referencing to measurements included in the ECG analysis datasets.

1.5 Can a CRO submit the ECG data on behalf of the sponsor or application owner?

The last Q&A in the ESG FAQ for processes provides instructions for CROs to submit data on behalf of their clients. These instructions require them to submit authorization from the application owner. However, going down this path is not recommended when considering the impacts to an eCTD application.

For example, for an application where submissions are required in eCTD (i.e. NDA/BLA/ANDA/Comm IND/DMF), the CRO and the application owner should think carefully about proceeding with an approach to submit directly to FDA instead of providing the information to the application owner for the owner to submit. The reason is because ECG waveform files are to be submitted in an eCTD sequence to the application and placed under the relevant study. The application owner or the owner's eCTD submission vendor have the previous eCTD sequence history submitted to FDA. These sequences are loaded in their eCTD publishing tool. If the CRO is making an eCTD submission but they did not make the previous eCTD submissions to the application then they would first need to get the previous eCTD sequences from the owner and then import into their eCTD publishing tool in order to create the next sequence before submitting to FDA. Further, they would need to provide that sequence to the application owner so the owner could then import it into their eCTD publishing tool so that they

maintain the full history of the application (which is needed when they make future eCTD submissions). In short, it would be easier for the CRO and application owner if the CRO could send the files to the application owner and let the application owner submit to FDA.

1.6 For which clinical studies is submission of annotated ECG waveforms recommended?

Digital ECG waveforms with annotations are usually submitted together with datasets supporting QT evaluation per ICH E14 guidelines. However, whether annotated ECG waveforms should be submitted for a given clinical study is a review issue. Please contact the project manager in the appropriate CDER review division if you have any questions.

1.7 Should a QT Evaluation Report Submission Checklist be included for Annotated ECG Waveform submission?

If the submission is not QT-related, then the QT Evaluation Report Submission Checklist is not needed. IRT strongly recommends sending this checklist to speed up the review process. The most recent version of the QT Evaluation Report Submission Checklist is available in IRT's website (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt).

1.8 Who should I contact with general ECG data submission questions?

Questions about general ECG data submissions may be directed to CDER at esub@fda.hhs.gov

2 Test submissions

2.1 Is it possible to perform a test submission?

Yes, it is possible to make test submissions through the ESG.

2.2 Who should I contact with questions about test submissions?

Questions about test submissions may be directed to CDER at esub@fda.hhs.gov

3 File formats

3.1 What are the accepted file formats for digital annotated ECG waveforms?

Digital ECG waveforms with annotations should be submitted in electronic format (XML) following the HL7 annotated ECG (aECG) standard. When submitting through the ESG, we recommend placing the ECGs in an aecg folder under the misc folder (e.g., m5 -> datasets -> [study-id] -> misc -> aecg).

3.2 Is it possible to submit continuous annotated ECG waveforms (i.e., Holter)?

Yes. Continuous ECG recordings (i.e., Holters) with annotations are supported by the HL7 annotated ECG (aECG) standard and could be submitted in electronic format (XML) following the HL7 annotated ECG (aECG) standard. You may contact esub@fda.hhs.gov if you have questions about your ECG data submission.

3.3 Should ECG waveforms include annotations?

It is recommended to submit digital ECG waveforms with annotations. For example, annotations in the ECG waveforms can be used to evaluate QT measurement bias and allow for cross-referencing to measurements included in the ECG analysis datasets.

3.4 Should the waveform files be grouped by site or by study?

ECG waveform files should be placed in the eCTD folder recommended in 1.3. Digital ECG waveforms with annotations in electronic format (XML) following the HL7 annotated ECG (aECG) standard should be grouped by study. However, scanned/digitized paper ECGs (see section 4 below) should be organized by site, subject or similar to reduce individual file size (e.g., scan all ECGs of one subject into one PDF with unique subject ID as part of PDF name).

4 When digital ECG waveforms are not available

For ECGs collected to support QT assessment per ICH E14, it is recommended to acquire high quality digital ECGs and submitting the digital ECG waveforms with annotations in electronic format (XML) following the HL7 annotated ECG (aECG) standard. The adequacy of the data collected in a study to be used for QT assessment will be a review issue.

4.1 Can scanned paper ECGs (e.g., PDF) be submitted?

Scan paper ECGs into PDF and submit to FDA only if digital ones are not available, preferably organized by site, subject or similar to reduce individual file size. When submitting through the ESG, we recommend placing the ECGs in an *aecg* folder under the *misc* folder (e.g., m5 -> datasets -> [study-id] -> misc -> aecg). For scanned/digitized paper (e.g., PDF) submissions: analysis datasets to support QT evaluation should include the automatic ECG measurements (i.e., as automatically generated by the ECG device in the clinical site without any adjustment).

4.2 Should paper ECGs be digitized and submitted as aECG XML files?

Scanned ECGs in PDF format can be submitted through the ESG without the need for digitization only if digital ones are not available. See FAQ 4.1 for details.