

Yale University Open Data Access (YODA) Project
Procedures to Guide External Investigator Access to Clinical Trial Data
Last Updated May 2016

OVERVIEW

These procedures support the YODA Project Data Release Policy and more fully describe the process by which clinical trial data held by a third party, often a medical product manufacturer that conducted the trial (or an academically-based clinical trialist) with whom the YODA Project has an agreement to serve in a decision-making role regarding the granting or denial of data requests, is made available to external investigators. The YODA Project's goal is to enhance data availability and transparency in support of strong scientific research which aims to advance scientific and medical knowledge with the ultimate goal of improving public health and healthcare delivery. These procedures were drafted to inform not only the YODA Project's partnerships with Medtronic, Inc. and Johnson & Johnson, but also to set standards that will apply to all similar future efforts.

Procedures for the following topics are described below:

1. Data Availability from Data Holder
2. YODA Project Data Request Requirements
3. YODA Project Review
4. Data Holder Due Diligence Assessment
5. YODA Project External Review
6. Data Use Agreement
7. Data Distribution

These procedures will be applied to all requests received by the YODA Project for access to available clinical trial data for independent scientific examination and addresses the processes needed to complete research proposal requirements, data receipt, data analysis, and dissemination of results. The YODA Project seeks to continually improve these policies and, accordingly, may modify the policy in the future.

1. Data Availability from Data Holder

Requests for redacted complete Clinical Study Reports (CSRs) or Individual Participant-Level Data (IPD) should be made to the YODA Project. While the YODA Project's objective is to review and decide upon Research Proposals, and when appropriate make all clinical trial data relevant to the particular Research Proposal available to external investigators, other legal and regulatory considerations may be considered by Data Holders in order to determine if they have legal and ethical rights to make the data available to external investigators for scientific purposes. The YODA Project may be unable to provide external access to clinical trial data in certain situations, including but not limited to:

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- The Data Holder does not have authority to provide the data to external investigators. For example, the Data Holder may not have authority because the medical product in question has been obtained from or has been developed in collaboration with an external partner (i.e., another medical product manufacturer) under a contract that does not permit or specifically prohibits external access to the data. In such a case, the YODA Project will request that reasonable effort be made by the Data Holder to work with the external partner to facilitate clinical trial data sharing.
- There are practical or feasibility constraints to providing data access related to resources such as costs or other issues. For example, the Data Holder may not have shareable data files if the requested data were generated many years ago; for instance, clinical trial data generated prior to 1990 may only be available in paper formats and not readily accessible to Data Holders as they have been placed in long-term storage facilities. Similarly, trials conducted in a foreign language may not be made available due to the associated costs of translation and redaction of materials. Additionally, Data Holders may need to consider the resources required to provide access to data and documents if the requested data are from a large number of products or trials and/or the data are housed in multiple legacy data systems and formats.
- The privacy and confidentiality of research participant data cannot be protected. For example, data from Phase 1 trials most often cannot be fully de-identified and redacted in such a way as to guarantee the anonymity of the research participants according to the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and European Union standards and are unlikely to be made available. Similarly, studies of rare diseases may have too few participants to prevent their de-identification. Protecting personal health information is of paramount importance; only data that can be appropriately de-identified will be shared.
- The clinical trial informed consent does not allow the sharing of de-identified data for research conducted by third parties (i.e., the researcher is neither a member of the Data Holder organization nor an affiliate). Some clinical trial informed consents may specify that clinical trial data cannot be used for research that is not directly related to the product studied or the condition / disease state studied in the trial, even if the researchers are from the Data Holder organization or an affiliate. However, in cases where conduct of research could benefit public health, it may be permissible to share de-identified data sets. Thus, a review of the informed consents, in the context of the proposed research, is essential in the determination of whether data can be shared or not. The YODA Project will work with Data Holders to modify informed consents for future clinical trials to permit the sharing of de-identified data for broader scientific, medical, and /or educational usage.

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- The Data Holder has not received regulatory approval for the medical product in question in both the U.S. and European Union. Clinical trial data that are part of an ongoing program for an initial regulatory submission or for a new indication of a marketed product in either the U.S. or European Union will not be made available to external investigators until after regulatory approval has been granted. Within one month of regulatory approval, data from otherwise available supportive trials can be made available to external investigators through the YODA Project.
- The Data Holder has not yet completed the trial (i.e., trial is ongoing) or the trial was completed too recently to share with external investigators. For example, Johnson & Johnson is committed to disseminating the results from its clinical trials in the peer-reviewed biomedical literature within 18 months after study completion. In this case, at 18 months after study completion, the data will be made available to external investigators through the YODA Project using the below described process and procedures.

In order to communicate data availability from the Data Holder, the YODA Project will develop and regularly update a publicly available listing of data assets already available in a secure data sharing platform. However, unlisted data can still be requested. Requestors will be able to submit inquiries about data availability prior to submitting a formal request (see **section 2: Data Request Requirements**). Requests for data that are not already listed as available on the YODA Project website will undergo a **Due Diligence Assessment** by the Data Holder (see **section 4: Data Holder Due Diligence Assessment**) to determine data availability.

2. YODA Project Data Request Requirements

The following information will be requested as part of the process to register to request data access through the YODA Project:

- Principal Investigator's name, degree(s), SCOPUS ID (if available), primary affiliation, and contact information, including phone, mailing address, and email address
- Other Key Personnel members' names, degrees, and SCOPUS IDs (if available)
- Funding source and conflict of interest statement (using a modified version of the ICMJE disclosure form) for the Principal Investigator and all Key Personnel
 - Requests that include independent funding will be considered, but are neither expected nor required
- Research Proposal, which includes project title, scientific abstract, brief project background and statement of project significance, specific aims, research methods, narrative summary, project timeline, dissemination plan, and bibliography [specific

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instructions are available on the YODA Project website]. In addition, requesting investigators should indicate the following:

- Data specification: which trial(s) are being requested
- Type of data requested: redacted complete CSRs or IPD
- Certification that the credentials and all information provided are true and that the requested data will not be used in pursuit of litigation or for commercial interests

3. YODA Project Review

All requests for data will undergo **Review** upon receipt by the YODA Project. The purpose of the Review is to ensure that the proposal has scientific merit, in that 1) the scientific purpose is clearly described; 2) the data requested will be used to create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health; and 3) the proposed research can be reasonably addressed using the requested data. During the Review, the YODA Project will evaluate submitted requests and associated registration materials to ensure that all required information has been provided. Proposals could include novel research using the data on secondary endpoints or subgroup populations, as well as research that confirms or validates previously conducted research.

Proposals submitted for non-scientific purposes, such as in pursuit of litigation or for commercial interests, will not be approved. Additionally, requests for research partnerships or other types of data, such as biological, pharmacological, radiographic, or genetic data, are beyond the scope of the YODA Project and will be returned to requestors. Requestors submitting incomplete or unclear requests for data access will be asked to revise their proposal and/or provide all required information.

All data requests and associated registration materials, including the Research Proposal and the YODA Project's decision to grant or deny data access, will be publicly posted.

4. Data Holder Due Diligence Assessment

Requests for data will also undergo a **Due Diligence Assessment** by the Data Holder. The primary purpose of the Due Diligence Assessment is for the Data Holder to provide the YODA Project with an assessment of its ability to make the data available to be shared externally, in line with the parameters set forth above (see **Section 1: Data Availability from Data Holder**), reviewing the Data Holder's legal and regulatory considerations in order to determine if they have legal and ethical rights to make the data available to external investigators for scientific purposes. However, the **Due Diligence Assessment** will also include estimation of the resources that would be required to make the data available to external requestors, such as the time and

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effort required to de-identify data in compliance with current regional standards to protect patient privacy and prepare the necessary accompanying documentation, providing an understanding of the technical considerations for the release of older clinical trial data that do not exist in an easily shareable format. The rationale for collecting this information is to broadly inform the field with estimates of resources required by Data Holders to make data available.

The **Due Diligence Assessment** will also include determination as to whether other researchers, either internally employed by or externally affiliated with the Data Holder, are engaged in similar research studies. The rationale for making this determination is so that external requestors are made aware of similar ongoing research efforts (so that there are no misunderstandings about generation of research ideas), as well as to foster collaborations. Requests for data that are already listed as available on the YODA Project website will undergo a **Due Diligence Assessment** by the Data Holder for this purpose only.

Lastly, the **Due Diligence Assessment** assesses whether the proposed research can be reasonably addressed using the requested data, including whether the variables needed for the proposed analysis are included in the requested data and whether the research question can be addressed using summary-level data.

Requests to access data will be approved if the requirements of the YODA Project's Review are met and the Due Diligence Assessment concludes that the data can be made available. All requests and associated registration materials, including the Research Proposal, a summary of the Data Holder Due Diligence Assessment, and the YODA Project's decision to grant or deny data access will be publicly posted.

5. External Review

An **External Review** is intended to solicit feedback from the YODA Project Steering Committee and other independent experts in the field if the YODA Project is unable to verify the scientific merit of the proposal.

The first step of External Review will be to solicit two independent peer reviews to evaluate the proposal's scientific merit, including whether 1) the scientific purpose is clearly described; 2) the data requested will be used to create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health; and 3) the proposed research can be reasonably addressed using the requested data. Reviews will be solicited from investigators with sufficient clinical expertise in the broader scientific community who are unaffiliated with the Data Holder or the YODA Project. Upon return of the independent, external reviews, the YODA Project will meet with at least one member of the YODA Project Steering Committee,

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who will also have independently reviewed all materials, in order to make a final decision to grant or deny data access. The YODA Project Steering Committee is an independent group of leaders in the fields of clinical research and biomedical ethics convened by the YODA Project to provide guidance.

All requests and associated registration materials, including the Research Proposal, a summary of the Data Holder Due Diligence Assessment, any scientific reviews from external investigators or the YODA Project Steering Committee, and the YODA Project's decision to grant or deny data access, will be publicly posted.

6. Data Use Agreement

Requestors must sign a Data Use Agreement (DUA) prior to receiving data. The decision to provide access to the data will be made by the YODA Project alone, although the Data Holder will retain the right to enforce any breach of the DUA as the rightful owner of the clinical trial data made available for external use. The stipulations and requirements of the DUA include:

- Signature by the Principal Investigator
- Signature by a representative of Yale University
- Acknowledgement of the Data Holder's rights to enforce the DUA
- Certification that the requestor's credentials and all information provided are true and that there are no debarment issues
- Certification that the requested data will not be used in pursuit of litigation or for commercial interests
- Agreement that no distribution of the data to third parties or public posting of the data will be permitted. The requestor must protect the confidentiality of the data, and may not copy, retransmit or reuse the data in any manner other than for the purpose described in the data request
- Acknowledgement that violations may be subject to all available legal remedies and will be posted on the YODA Project Website
- Agreement that the Principal Investigator (or any other permitted data user) will not attempt to re-identify individuals within the clinical trial data
- Agreement that the scope of the analyses will be limited to the specific aims set out in the proposal; additional research objectives will require the submission of a new proposal or an amendment to the previously approved proposal
 - Amendments to the previously approved proposal will be linked to the unique application identification number provided by the YODA Project
- Agreement that any unexpected or serious safety findings must be reported to the Data Holder immediately for further evaluation and reporting to appropriate health or regulatory authorities

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- Agreement that any public dissemination of the findings resulting from the proposed research will be required to take place through peer-reviewed publication in the biomedical literature or at a scientific meeting. Once published, findings can be disseminated in any additional media venue. In addition, no press release shall be issued by the data requestor summarizing the research findings unless made under embargo in concert with publication through a peer-reviewed publication in the biomedical literature or at a scientific meeting.
- Agreement that all public dissemination of the findings will be required to include standardized language that reflects that the analyses were based on data made available via the YODA Project and include a link to the unique application identification number
 - This specific statement must be referenced in all dissemination of findings: “This study, carried out under YODA Project # XXXX, used data obtained from the Yale University Open Data Access Project, which has an agreement with [Data Holder]. The interpretation and reporting of research using these data are solely the responsibility of the authors and does not necessarily represent the official views of the Yale University Open Data Access Project or [Data Holder].”
- Agreement that the investigator will provide the YODA Project a copy of any abstract and manuscript generated from the data request at the time of submission to a scientific research meeting or a biomedical journal. The YODA Project will share this copy with the Data Holder upon receipt. Neither the YODA Project nor the Data Holder will have the authority to approve, reject, or revise the investigator’s work. Advanced notification may help to identify any relevant safety issues that should be reported to appropriate regulatory officials.
- Acknowledgement of an expiration date of one year after signing the DUA, which can be renewed by the YODA Project for additional one-year periods for ongoing projects
- Acknowledgement that the investigator will retain the rights to access data for an additional five years for completed projects for the express purpose of verification of the investigator’s publication and to respond to inquiries regarding the publication
- Agreement that the investigator will provide the YODA Project with a report describing the results of the research at the time that the research is completed. The YODA Project is free to publicly post the results after DUA expiration with appropriate acknowledgment of Data User.
- Agreement that log-in credentials used to access the secure data sharing platform will be kept confidential

7. Data Distribution

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Once the DUA is signed by all parties, the data will be made available to approved data requestors. The method by which data will be made available will depend on the Data Holder.

One possible method will involve data being made available to approved requestors via a password-protected personalized account on a secure (Safe Harbor) data sharing platform. For those Data Holders preferring this method, access will be granted to a maximum of three researchers per approved data request. All relevant clinical trial data and supporting documentation will be made available via this platform, including the following (which have been appropriately de-identified or redacted to protect patient privacy):

- Collected participant-level data sets
- Annotated case report forms
- Data set specifications
- Protocols with any amendments
- Reporting and analysis plans
- Complete clinical study reports

Data will remain on the secure Safe Harbor platform and will not be downloadable or copied. However, relevant associated materials, such as clinical study reports and protocols, will be downloadable from the secure Safe Harbor platform. In addition, requests granted solely for redacted complete CSRs will be distributed directly, without access through the secure Safe Harbor platform.

For requests approved to access participant-level data sets, all work on the data must take place within the secure platform. The platform will be easily accessible to researchers, and ongoing system monitoring and support will be available. Within the platform, researchers will have access to analytical tools, such as SAS, SAS Visual Analytics, and R. If needed, researchers will be able to upload additional data sets to the secure platform. The YODA Project will work with researchers to ensure that projects can be conducted within the platform.

Although not routine, if there are requests that require data dissemination outside of the secure data sharing platform, these will be considered and evaluated on an individual basis. This option will only be considered after all attempts have been made to facilitate the approved research within the secure data sharing platform.

Another possible method for providing data access to approved requestors involves transfer of data directly to the requestor via a secure electronic data transfer system (after the DUA has been signed by all parties). Depending on the system, these data may need to be downloaded in order to be used.

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Regardless of the data access method, support of the investigative teams will be provided as is feasible. The YODA Project can facilitate contact between Data Users and Data Holders, if consultation is desired on the part of the Data User. The consultation is voluntary and at the discretion of the Data User.

In addition, questions can be submitted to the YODA Project through the Data Request website; one member of the YODA Project will review each submitted question, determine whether it is answerable with available resources, and provide a response. Questions will not be routinely forwarded to the Data Holder for clarification except under special circumstances and at the full discretion of the YODA Project.

Researchers receiving the data will be accountable for complying with this policy and the DUA. Compliance among the investigative teams to the DUA will be monitored by the YODA Project and the Data Holder. The YODA Project will engage in surveillance efforts to determine if the Principal Investigator has followed this policy, appropriately amended the research proposal, reported results, included required language and unique application identification number in any publication of findings, and discontinued analysis after DUA expiration.

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Glossary of Key Definitions:

Clinical Study Report (CSR): A formal report that provides a comprehensive description of the design, methods, and results of a clinical trial. A CSR can be short (“abbreviated”) or several thousand pages long.

CSR Summary: A brief overview summarizing the study plan and results, including a numerical summary of efficacy and safety results, study objective, criteria for inclusion, methodology, etc.

Data Holder: Clinical trial data is often held and/or controlled by one party which designed, conducted and/or funded the clinical trial, often a medical product manufacturer, an academically-based clinical trialist, or a government-based funder of clinical trials

Data Use Agreement (DUA): Document signed by the Principal Investigator that includes attestations related to confidentiality, subject re-identification, public dissemination, and data use expiration, and such other terms as set forth in Section 6 above, that ensures responsible conduct of research and good stewardship of the data

Data User: An investigator who receives de-identified data for analysis under the YODA Project Data Use Agreement

De-identified Data: Health information that does not allow for the identification of an individual and for which there is no reasonable basis to believe that the information can be used to identify an individual. Health information is considered sharable when appropriately de-identified as per current regional standards to protect patient privacy. At a minimum, health information is considered de-identified 1) if stripped of all of the 18 direct identifiers defined under the Health Insurance Portability and Accountability Act (HIPAA), or 2) if an expert in statistical and scientific method determines that there is a very small risk that the information could be used alone or in combination with other information to identify an individual. In addition, all trial site IDs and patient IDs will be re-randomized and the randomization code destroyed.

Debarment Issues: Federal regulatory and contracting issues which prohibit potential Data Users to gain access to clinical trial data through the YODA Project, including individuals:

- (i) Excluded from a Federal health care program as outlined in Sections 1128 and 1156 of the Social Security Act (see the Office of Inspector General of the Department of Health and Human Services List of Excluded Individuals/Entities at <http://www.oig.hhs.gov/Fraud/exclusions/listofexcluded.html>);
- (ii) Debarred by the FDA under 21 U.S.C. 335a (see the FDA Office of Regulatory Affairs Debarment List at http://www.fda.gov/ora/compliance_ref/debar/); or

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(iii) Excluded from contracting with the federal government (see the Excluded Parties Listing System at <http://epls.arnet.gov>).

Due Diligence Assessment: An assessment performed for requests for data that are not available in the secure data sharing platform. Due Diligence Assessment includes an evaluation by the Data Holder of its ability to make the data available to be shared externally, including resources required to make requested data available to external researchers and considerations such as the time and effort required to make data available in compliance with all requirements, prepare necessary accompanying documentation, and technical considerations for the release of older clinical trial data that do not exist in an easily shareable format. The Due Diligence Assessment will also include determination as to whether other researchers, either internally employed by or externally affiliated with the Data Holder, are engaged in similar research studies. Requests for data that are already listed as available on the YODA Project website will undergo a Due Diligence Assessment by the Data Holder for this purpose only.

External Review: Review to solicit feedback from external experts in the scientific field and/or the YODA Project Steering Committee to gain additional perspectives on the scientific and public health importance of the research proposal. External Review may be invoked when there is any question of the scientific merit of the proposal for which the data have been requested.

HIPAA: Health Insurance Portability and Accountability Act of 1996 (as amended). A Federal law that includes privacy and security standards for health information created, received, stored, or transmitted by covered entities such as health plans, health care providers, and health care clearinghouses. More information is available at <http://www.hhs.gov/ocr/privacy/>.

Individual Participant-level Data (IPD): Individual participant data collected on each study subject at each visit or study contact. Participant-level analyzable data are in databases that allow analysis by computer programs and statistical tests.

Key Personnel: Any individual collaborating with the Principal Investigator that contributes to the scientific development or execution of the project in a substantive or measurable way

Principal Investigator: The individual responsible for directing the research project and who ensures the proper conduct of the project

Redacted Data: Data from which any confidential or private information that could permit re-identification of participants, investigators, or study locations has been removed

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Research: A systematic investigation, including development, testing and evaluation, designed to contribute to generalizable knowledge

Research proposal: Document submitted to the YODA Project for data access describing the research plan. Sections of the research proposal include project title, scientific abstract, brief project background and statement of project significance, specific aims, research methods, narrative summary, project timeline, dissemination plan, and bibliography. The Proposal also includes a description of the specific trials to be analyzed and whether Clinical Study Reports or Individual Participant-Level Data are requested.

Resources: The time and cost required to fulfill a data request (see: **Due Diligence Assessment**)

Review: All data requests will undergo the YODA Project Review to ensure that the proposal has scientific merit, in that 1) the scientific purpose is clearly described; 2) the data requested will be used to create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health; and 3) the proposed research can be reasonably addressed using the requested data. Proposals related to litigation or for commercial purposes will not be approved.

Safe Harbor (Data Sharing) Platform: A password-protected personalized account on a private server housing all relevant clinical trial data that is enabled with analytical tools and allows online statistical analysis. Data are considered to be in Safe Harbor when they have been appropriately de-identified and there is no reasonable basis to believe that the remaining information could be used to identify a person. Data in Safe Harbor are able to be readily shared with external investigators, along with all appropriate documentation.

Scientific Review: An assessment that the research proposal has scientific merit, in that 1) the scientific purpose is clearly described; 2) the data requested will be used to create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health; and 3) the proposed research can be reasonably addressed using the requested data

Serious Safety Finding: A result following the statistical analysis of data that points to an increased potential for risk of the drug or any contradiction of the current drug labelling