## Online Supplementary Appendix

## Figures and Screenshots (from 1 February 2018)

**Figure S1: Accessing Archival Versions of a ClinicalTrials.gov Study Record via "History of Changes."** (A) Click on the History of Changes link near the bottom of a study record in the "Study Details" format to access previously posted versions of that record. (B) On the ClinicalTrials.gov archive site, select the two versions to view and click "Compare." By default, the record as initially registered (i.e., "Version 1") and the most recent version that is currently displayed on the public site are selected.

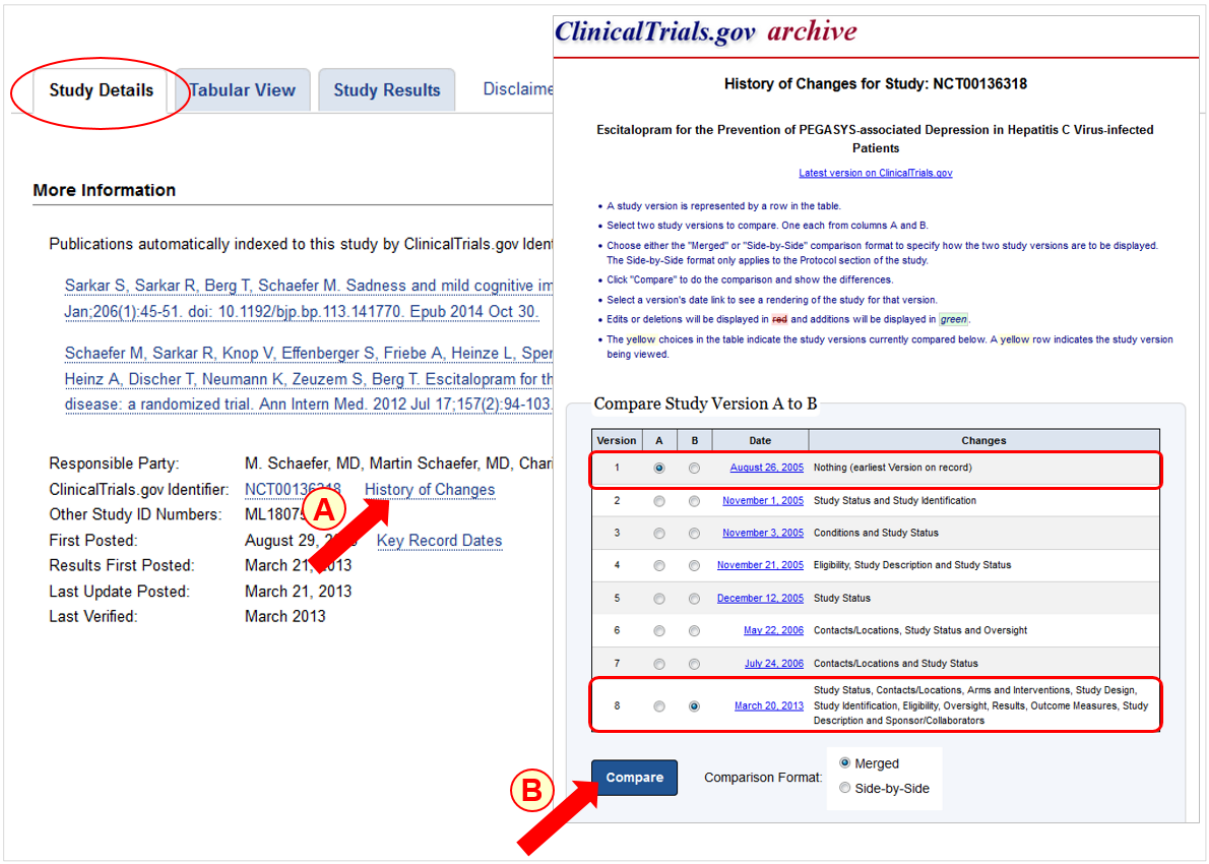
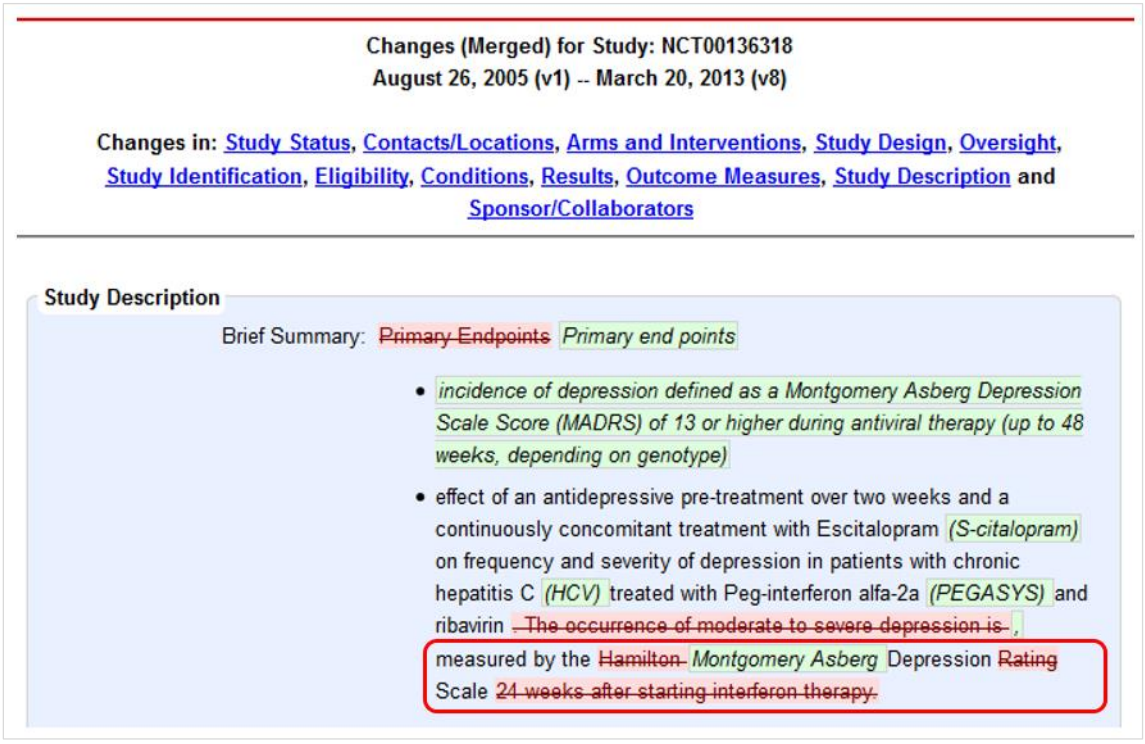


**Figure S2: Viewing Changes in Archival Versions of a ClinicalTrials.gov Study Record**. Entries and text displayed in the earlier version but deleted from the later version are shown with red strikeout. Those displayed in the later version only are shown in green-highlighted, italicized font. For example, under the second bullet of the Primary Outcome Measure, "Hamilton Depression Rating Scale" was changed to "Montgomery Asberg Depression Scale." [See Zarin & Tse (2013)]



**Changes (Merged) for Study: NCT00136318**
**August 26, 2005 (v1) -- March 20, 2013 (v8)**

**Changes in:** Study Status, Contacts/Locations, Arms and Interventions, Study Design, Oversight, Study Identification, Eligibility, Conditions, Results, Outcome Measures, Study Description and Sponsor/Collaborators

**Study Description**

Brief Summary: ~~Primary Endpoints~~ *Primary end points*

- *incidence of depression defined as a Montgomery Asberg Depression Scale Score (MADRS) of 13 or higher during antiviral therapy (up to 48 weeks, depending on genotype)*
- effect of an antidepressive pre-treatment over two weeks and a continuously concomitant treatment with Escitalopram *(S-citalopram)* on frequency and severity of depression in patients with chronic hepatitis C *(HCV)* treated with Peg-interferon alfa-2a *(PEGASYS)* and ribavirin ~~. The occurrence of moderate to severe depression is~~ , measured by the ~~Hamilton~~ *Montgomery Asberg* Depression ~~Rating~~ Scale ~~24 weeks after starting interferon therapy.~~

**Figure S3: Viewing Changes in Outcome Measures of a ClinicalTrials.gov Study Record via the "Tabular View."** The Tracking Information section of a study record in the "Tabular View" format displays for outcome measures the (A) original entry as first registered and (B) the most recent (current) entry and the date on which it was submitted. In this example, no secondary outcome measures were submitted during the initial registration.

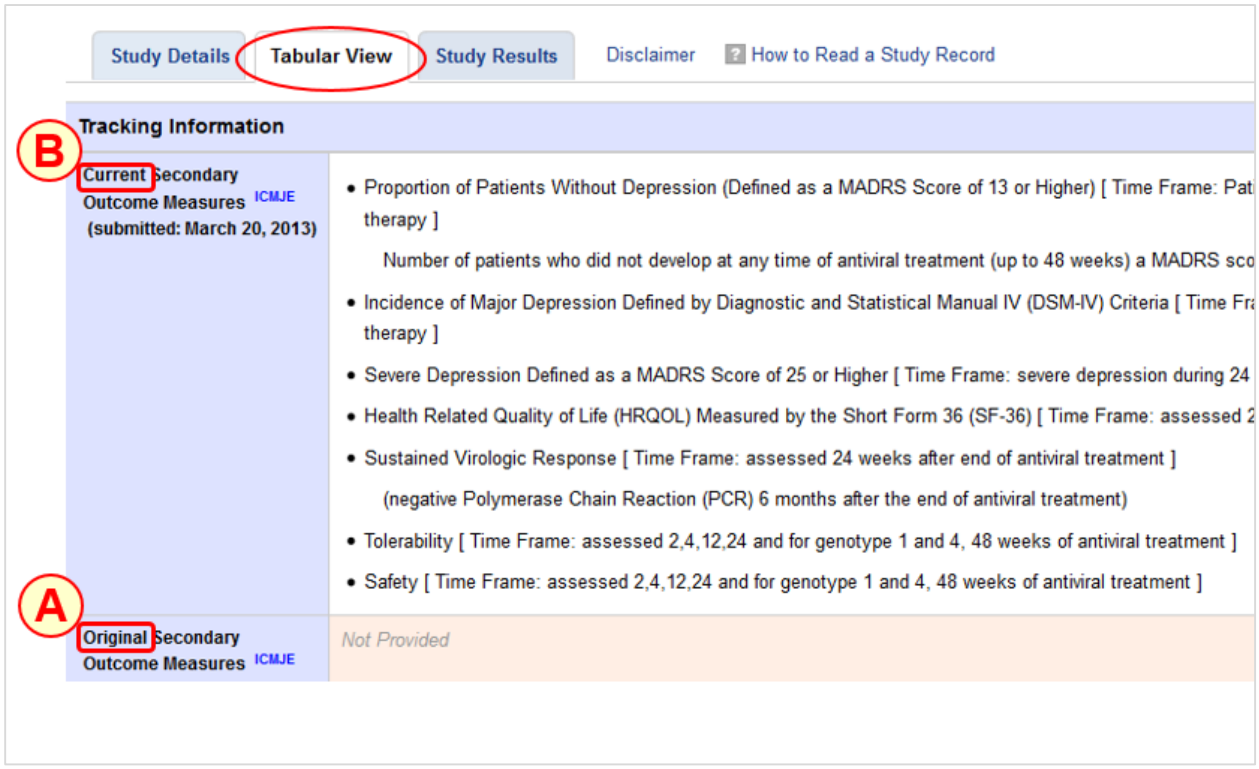


**Figure S4: ClinicalTrials.gov Basic Fielded Search Form.** Provides several key search fields.

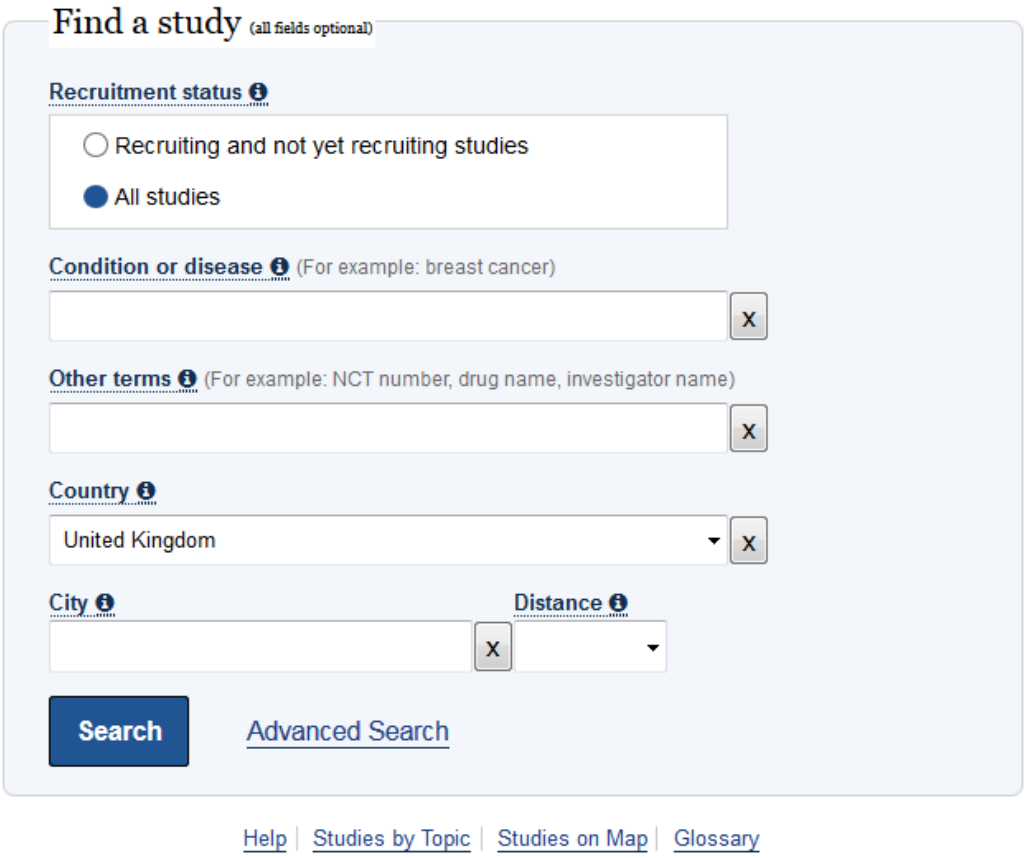


**Figure S5: ClinicalTrials.gov Advanced Search Form**. Provides many more search fields.

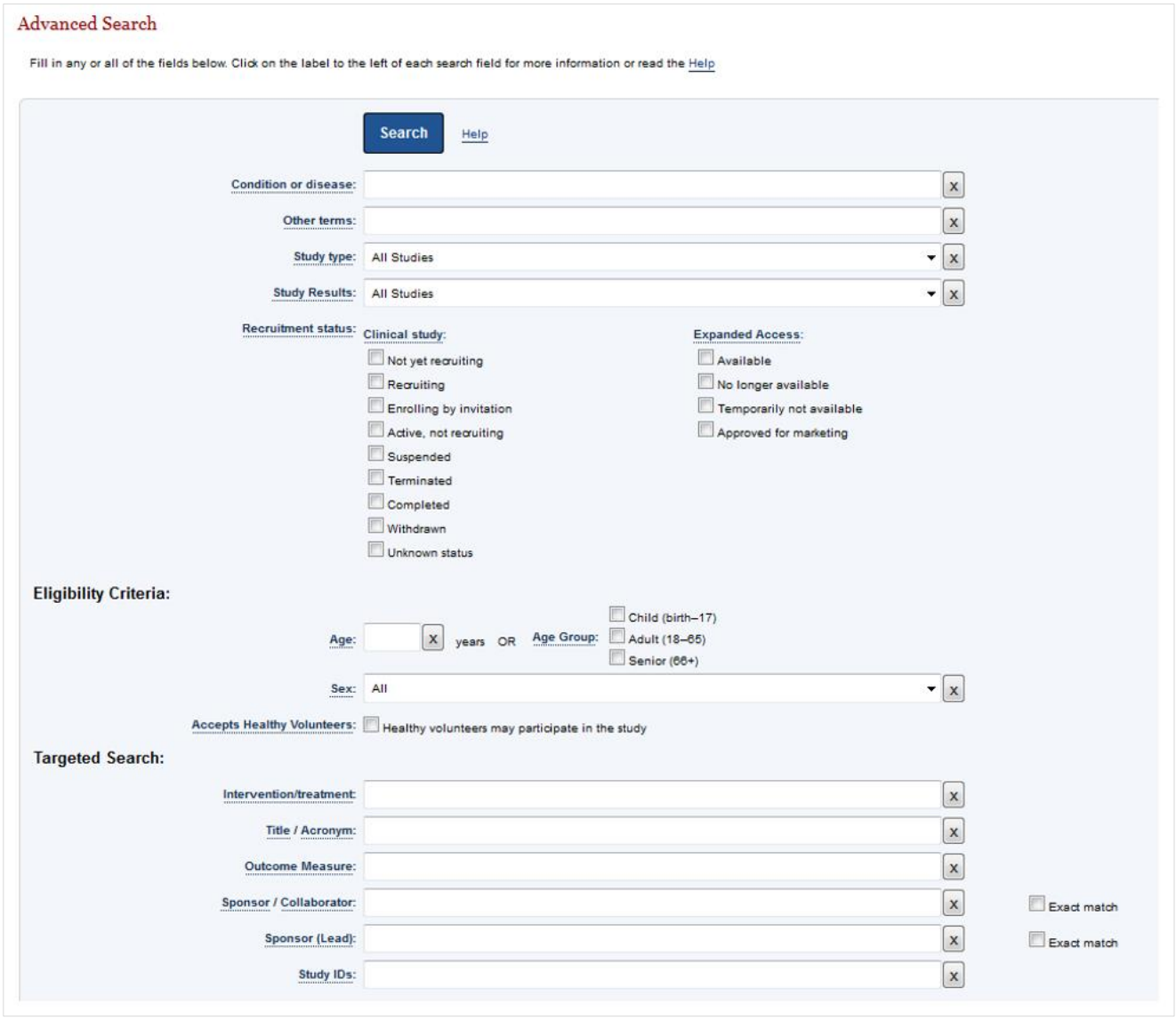


**Figure S6: Download the Search Results Panel**. After conducting a search, (A) clicking on "Download" opens (B) a new window that provides options for downloading the retrieved records including number of study records, data elements, and file format.

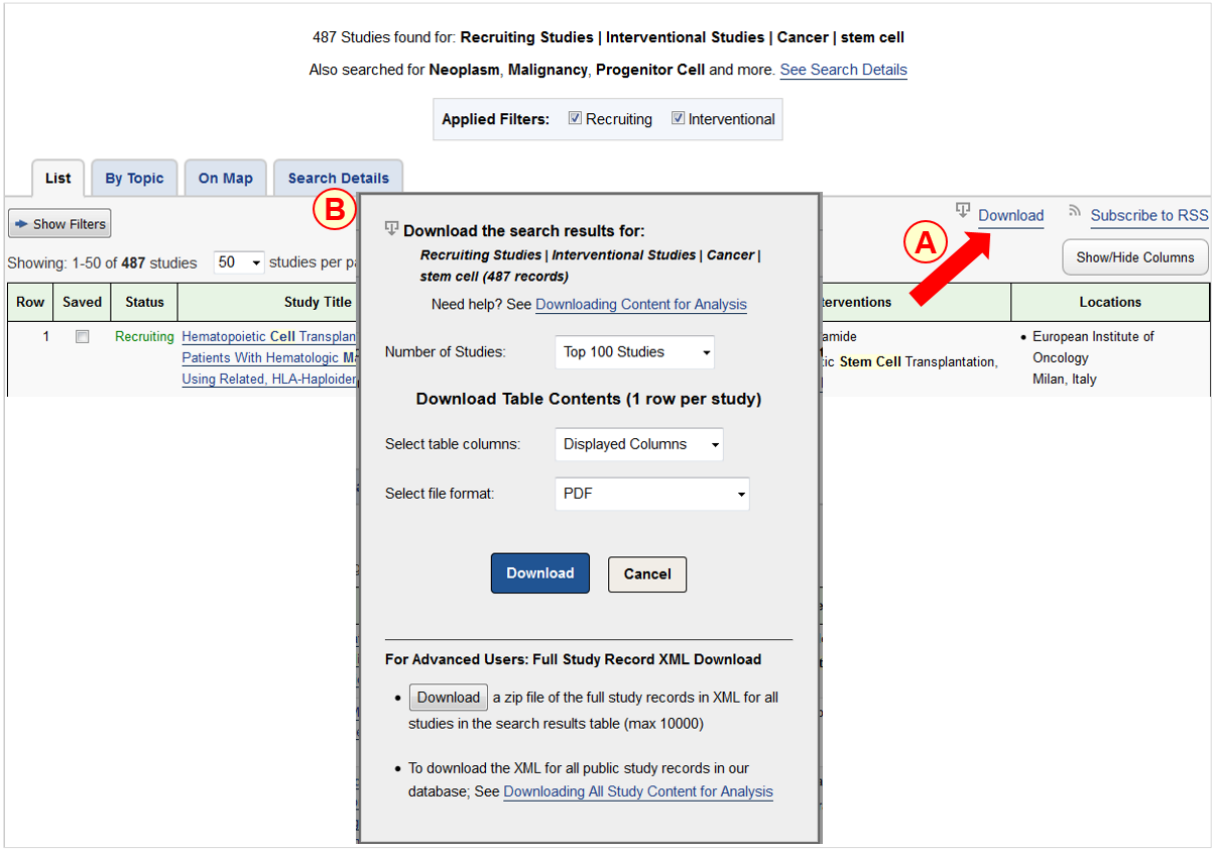


**Table S7: Content of a ClinicalTrials.gov Record for Interventional Studies: Overview of Minimum Information Requirements for (A) Registration and (B) Results Reporting by Data Element***

| (A) Required Registration Data Element |
|---|
| **Trial Identification and Key Dates**<br>• Brief Title, Acronym, Official Title[WHO]<br>• Study Type[WHO]<br>• Key Dates<br>  ○ Study Start Date[WHO]<br>  ○ Primary Completion Date<br>  ○ Study Completion Date[WHO] |
| **Key Protocol Details**<br>• Brief Summary<br>• Study Design<br>  ○ Primary Purpose, Study Phase, Interventional Study Model, Number of Arms, Masking, Allocation, Enrollment[WHO]<br>• Arm Information – for each: Arm Title, Arm Type[WHO]<br>• Primary Disease or Condition[WHO]<br>• Interventions – for each: Intervention Type, Intervention Name, Intervention Description[WHO]<br>• Primary and Secondary Outcome Measures – for each: Title, Description, Time Frame[WHO] |
| **Oversight Information**<br>• Responsible Party, by Official Title<br>• Studies a U.S. FDA-regulated Drug Product<br>• Studies a U.S. FDA-regulated Device Product, Device Product Not Approved or Cleared by U.S. FDA, Pediatric Postmarket Surveillance of a Device Product<br>• U.S. Food and Drug Administration IND or IDE, FDA Center, IND/IDE Number, IND Serial Number (Not publicly displayed)<br>• Availability of Expanded Access, Expanded Access Record NCT Number<br>• Product Manufactured in and Exported from the U.S.<br>• Human Subjects Protection Review Board Status |
| **Recruitment Information**<br>• Overall Recruitment Status, Why Study Stopped[WHO]<br>• Eligibility Criteria[WHO]<br>  ○ Sex/Gender Based<br>  ○ Age Limits<br>  ○ Accepts Healthy Volunteers<br>  ○ Inclusion and Exclusion Criteria<br>• Central Contact Person (or Facility Contacts at each location)<br>• Facility Information – for each facility:<br>  ○ Name and Address[WHO]<br>  ○ Individual Site Status<br>  ○ Facility Contact (or Central Contact Person) [WHO] |
| **Administrative Information**<br>• Unique Protocol Identification Number[WHO]<br>• Secondary IDs and Type[WHO]<br>• Name of the Sponsor[WHO]<br>• Record Verification Date |

**(B) Required Results Reporting Information**

**Participant Flow,** by arm

- Started – Number of participants that entered the study
- Completed – Number of participants that finished the study
- [Not Completed – Computed number of participants that started but did not complete the study (e.g., dropped out of the study]

**Baseline Characteristics**, by arm and overall

- Age
- Sex/gender
- Race and ethnicity (if collected under the protocol)
- Other study-specific measures

**Outcome Measures –**
**For each pre-specified primary and secondary outcome measure:**

- Name of Measure – for each: Type, Title, Description
- Unit of Measure
- Time Frame – Time point(s) at which the measurement was assessed for the specific metric used
- Total and by arm:
  - Outcome data
  - For continuous measures, also measures of central tendency, measure of dispersion/precision
  - For categorical measures, also name of category, value for each category

**Statistical Analyses per Outcome Measure– For each provided:**

- Overview: Comparison groups selected for comparison, Type of statistical test (e.g., superiority, non-inferiority)
- Either of:
  - Statistical Test of Hypothesis (*if provided*): P-value, Method name (e.g., ANCOVA, chi-squared) OR
  - Method of Estimation (*if provided*): Estimation parameter name (e.g., Cox proportional hazard, mean difference (final values), Confidence interval )e.g., 95%, Number of sides (1 or 2), Lower limit, Upper limit)

**Adverse Event Information**
**All-cause mortality, by arm:**

- Total number of participants who died due to any cause
- Total number of participants included in the assessment of deaths due to any cause (i.e., denominator for calculating frequency of all-cause mortality)

**For each serious adverse event:**

- Adverse event term
- Organ system
- Collection approach (systematic or non-systematic assessment)
- Adverse event data, by arm:
  - Number of participants affected
  - Number of participants at risk

**Other adverse events:**

- Frequency Threshold for Reporting, by arm (e.g., 5%)
- For each other adverse event:
  - Adverse event term
  - Organ system

| |
|---|
| ○ Collection approach (systematic or non-systematic assessment)<br>○ Adverse event data, by arm:<br>▪ Number of participants affected<br>▪ Number of participants at risk |
| **Uploaded Study Documents**<br>**For each document saved as a PDF/A file:**<br>• Document type (e.g., study protocol)<br>• Document date and subtitle<br>• Document |
| **Other Information**<br>• Results point of contact<br>• Certain agreements that restrict PIs from discussing the results of a study after completion |

*For a complete listing, see Data Element Definitions, Templates, and Checklists (https://clinicaltrials.gov/ct2/manage-recs/resources#DataElement)
WHOData elements also required by the WHO ICTRP Trial Registration Data Set.

**Table S8: Key Changes to the Structure and Requirements for Selected Data Elements**

| Data Element | Description of Change in Structure or Requirement | Data Element Status | Month/Year |
|---|---|---|---|
| Primary and Secondary Outcome Measures | First introduced as a free-text field | Optional | September 2004 |
| | Definitional changes, including adding information about the timeframe | Optional | May 2005 |
| | Split up into 3 distinct sub-elements:<br>1. Outcome Measure<br>2. Time Frame: "The duration of making measurements"<br>3. Safety Issue (Y/N): "Is this outcome measure assessing a safety issue" | Optional | December 2007 |
| | "Description" free-text field added as sub-element | Optional | February 2010 |
| | Change in status: Title and Time Frame sub-elements required "for records first released on or after December 1, 2012" | Required (Title and Time Frame) | December 2012 |
| | Change in status: Description sub-element required "if Study Start Date is on or after January 18, 2017" | Required (Title, Description, and Time Frame) | January 2017 |
| Primary Completion Date | First introduced as "Completion Date" with Month/Year format | Optional | December 2007 |
| | Renamed "Primary Completion Date" | Optional | January 2008 |
| | Change in status: required "for records first released on or after December 1, 2012 | Required | December 2012 |
| | Format changed to Month/Day/Year | Required | January 2017 |
| Study Start Date | First introduced as "Start Date" with Month/Year format | Optional | September 2004 |
| | Name changed to "Study Start Date" | Optional | October 2004 |
| | Change in status: required "if Study Start Date is on or after January 18, 2017" and format changed to Month/Day/Year | Required | January 2017 |

**Box S9: Helpful Hints for Researchers**. Practical and technical tips for applying the 10 issues to consider and examples.

**1. ClinicalTrials.gov includes more than "clinical trials"**

- Researchers can use a Filter on the Search Results page or the Advanced Search form to limit records by Study Type.
- Researchers should be aware, however, that searching by any parameter(s) without using the Study Type filter will retrieve records across all study types. For example, searching by a drug name will yield interventional, observational, and expanded access records.

**2. Follow-on studies may be registered as separate records**

- Researchers may find separate records for studies that might informally be referenced as a single "study" by the study sponsors. For example, protocol #01-M-0192 is registered as two separate records to represent both an "interventional" component (NCT03283930, a randomized controlled trial) and an "observational" component (NCT00018057, an observational study). The records represent studies in different populations and with different analyses for understanding anxiety in children and adolescents by the same researchers.
- Similarly, a single registered study may have results reported in multiple publications. For example, NCT00047385 (The National Lung Screening Trial or NLST) is linked to multiple publications, including articles reporting results from the initial screening examination, analysis of agreement in a retrospective reading of NLST screening chest radiographs, results of two incidence screenings, and a retrospective cohort analysis of NLST participants among others.

**3. Incentives for reporting trials change over time**

- Researchers should be familiar with the different reporting requirements (for more information, see links under "Key Policies" in Table 1 and Table 2)

**4. ClinicalTrials.gov includes mandatory and optional data elements**

- Researchers need to recognize when a data element (or sub-element) was added, changed, or deleted.

**5. ClinicalTrials.gov conducts quality control review**

- Researchers should understand the ClinicalTrials.gov quality control (QC) review criteria for making valid assessments about the studied records.
- Researchers should be aware that changes in QC review criteria may result in differences in specificity of the information submitted for data elements over time.

**6. Records can be modified by the responsible party at any time**

- The date on which ClinicalTrials.gov was searched and analyzed should be reported in any publications.
- Researchers who plan to reuse record information should download their analysis sample for future use and documentation.
- Researchers should consider whether the current version of each data element or some earlier version is most relevant to the analysis (e.g., the current primary outcome measure, which may incorporate updates since initial registration, or the version as originally registered).
- Researchers should understand how and what information might have changed within each study record during the study period.

**7. ClinicalTrials.gov does not have all information for all studies**

- Researchers need to assess the impact of the potential for missing studies from the CRE on the representativeness of any sample they choose.
- Researchers need to consider the impact of missing responses for data elements (e.g., whether or not the analysis population should include studies of interest that do not have responses for that data element)

**8. ClinicalTrials.gov data can be accessed in several ways**

- Researchers should consult the Downloading Content Analysis page (https://clinicaltrials.gov/ct2/resources/download) for more information.

**9. Defining a sample of records to answer a specific question**

- Researchers need to consider what type(s) of studies they want to include in their sample.
- Researchers need to consider to what degree the study type and design for studies of interest are covered by the scope of ClinicalTrials.gov, and how the scope has evolved over time. For instance, due to federal requirements, non-phase 1 trials of FDA-regulated drug, biological, and device products are represented more fully and systematically in ClinicalTrials.gov than other therapies, such as behavioral interventions, dietary supplements, and medical procedures.
- Researchers need to consider the reporting policies that apply to studies within a geographic region of interest. For example:
    - When analyzing trial locations, or considering changes over time to trials' geographic distribution, researchers should consider the evolution of rules and policies affecting reporting throughout the regions.
    - Additionally, sponsors and investigators can remove location information after a study ends, but information at the country level is maintained in the record's Tabular View (as "Removed Location Countries") and full facility information is available in the Archive site.
- Researchers should also consider which of the several potential date fields within the database are most appropriate and relevant to the research question and analyzed time-period, including the implications of each date (e.g., Primary Completion Date versus Study Completion Date).

**10. Using the ClinicalTrials.gov results database**

- Researchers should consult the following resources for more information:
    - About the ClinicalTrials.gov Results Database page (https://clinicaltrials.gov/ct2/about-site/results)
    - Results Data Element Definition document (https://clinicaltrials.gov/ct2/manage-recs/resources#DataElement)
    - Results QC Review Criteria document (https://clinicaltrials.gov/ct2/manage-recs/resources#ReviewCriteria)
    - How to Find Results of Studies page (https://clinicaltrials.gov/ct2/help/how-find/find-study-results)