

Documenting Concomitant Medications in Clinical Trials

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A concomitant medication (con-med) is a drug or biological product, other than a study drug, taken by a subject during a clinical trial. The protocol normally defines a specific reporting period in which the subject's use of con-meds is documented, e.g., from 60 days prior to signing the informed consent until the last study visit. The study protocol normally specifies how study sites should record a subject's concomitant medications. These specifications may be augmented by other written instructions, such as in a Case Report Form (CRF) Completion Guide. However, the manner in which study sites record con-meds is not always accurate and unambiguous.

This article will review basic principles of concomitant medication documentation and provide recommendations based on relevant regulatory requirements and guidance, along with examples, for a standardized methodology to create an accurate and unambiguous record in a CRF.¹⁻⁶

The Food and Drug Administration (FDA) definitions are as follows:⁷

Drug:

- A substance recognized by an official pharmacopoeia or formulary.
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.
- A substance (other than food) intended to affect the structure or any function of the body.
- A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.
- Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process).

Biological Product:

Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources – human, animal, or microorganism – and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.

Most countries consider dietary supplements, nutraceuticals and vitamins as special categories of food, not drugs. However, it is customary in clinical research to record these items on the con-med page of the CRF.

A medication is referred to either by its **generic name** or its **trade name**. The generic name describes the drug substance, while the trade name is the advertised brand name under which the drug is sold.⁸ Subject to sponsor requirements, both generic and trade names may be utilized when documenting con-meds. However, the generic name is generally preferred because of its specificity. An International Nonproprietary Name (INN) is the official non-proprietary, generic name given to a pharmaceutical substance by the World Health Organization (WHO). INNs were developed to facilitate communication by providing a standard name for each substance.

In some instances, drugs have generic names with and without numeric components, e.g., 6-mercaptopurine and mercaptopurine. In cases like this, it is best to use the name without the numeric component because 6-mercaptopurine may be misinterpreted as six units of mercaptopurine. In general, avoid drug name abbreviations such as 5-ASA, MTX and HCTZ, because they can be misinterpreted as well.

Clinical trial subjects often do not remember their con-med names and doses, so ask them to bring their pill bottles to the study visit.

The **indication** for a medication is the reason for which it is used, i.e., for treatment, prophylaxis, diagnosis, mitigation or cure of a condition or disease. A common problem in clinical research is the use of different terminologies for the condition involved when an Adverse Event (AE) and its corresponding con-med are documented. This inconsistency requires time-consuming reconciliation by the sponsor later in the trial. The terminology used for the CRF medication entry should therefore match as close to verbatim as possible to the historical condition or AE being treated. Otherwise, it should describe the specific intent, i.e., prophylaxis, diagnosis, mitigation or cure.

"The word **prophylaxis** is from the Greek and means 'an advance guard.'" ⁹ Taking an antibiotic prior to surgery to prevent a possible infection is an example of a prophylactic use. Another example of a prophylactic use is taking an antibiotic for a prolonged period following the resolution of an infection in order to prevent reoccurrence. Vaccines can be prophylactic as well.

"The word **diagnosis** is derived from the Greek words 'dia' which means 'by', and 'gnosis' which means knowledge." ¹⁰ A physician may give a medication to a patient to help diagnose the patient's condition. For example, Colchicine can be used to confirm if a subject has gout.

Mitigation serves "to make milder or more gentle; mollify; appease." ¹¹ For example, intravenous mannitol has been shown to minimize nephrotoxicity induced by amphotericin B.

A **Cure** is a successful treatment of a disease or a medicine or therapy that cures a disease. For example, biologics are used in gene therapy to cure various diseases.

The **dose** or **dosage** denotes a quantity of a medication prescribed to be taken at one time or at stated intervals.¹²

List the amount of the con-med in a single entry on the CRF. However, if the dose varies within a limited range, you can also document the range, e.g., 1-2 tabs or 200-400 ml, in a single entry. If the dosage changes at a point in time, make a new entry. If the medication is used in a predefined tapered or other mixed dosage regimen, you can document the entire course of the treatment in a single entry. Do not place a decimal and a zero after a whole number, e.g., use 2 mg rather than 2.0 mg, because individuals working from copies

may not see the decimal point, causing a tenfold discrepancy. For a similar reason, enter doses less than one unit with a zero before a naked decimal, e.g., 0.5 ml rather than .5 ml.

A medication **unit** is the term used to denote its amount. The metric system, e.g., mg, kg, mcg, ml is generally used. Other systems such as the international unit may be used as well. The **international unit (IU)**, alternatively abbreviated **UI**, from the French unité internationale) is a unit of measurement in pharmacology for the amount of a substance, based on measured biological activity (or effect).¹⁰ It is used for vitamins, hormones, some drugs, vaccines, and blood products.

When documenting a con-med, use only a single unit per line entry. Avoid entries such as 1 tab/100 mg but enter the most accurate unit for the medication, e.g., 100 mg. Do not abbreviate the word "unit" because the handwritten "u" can look like a 0 (zero).¹³ "IU" is not a safe abbreviation for international units because the handwritten "IU" can look like "IV"; therefore, write out "international units" or use "int. units." Insert a space between a number and its units for ease of reading, e.g., "10 mg" rather than "10mg."¹³ Do not abbreviate microgram as "ug"; instead use "mcg" to minimize the chance of misinterpretation.¹³

Avoid using the apothecary system of measures – the grain (abbreviated "gr") for weight and the minim (abbreviated "m") for volume – because it is becoming obsolete.¹⁴ During the first half of the 20th century, the apothecary system was replaced by the metric system. If a con-med is encountered with an apothecary system unit, convert it to a common measurement form, e.g., metric unit such as the milligram (mg).

The **start/stop date** of a medication is the timeframe in which the medication was or is being used. The sponsor may specify how dates are to be recorded. If not, state them in a complete month/day/year or day/month/year format. Always try to get the complete date(s) of use of a medication through communication with the subject rather than an estimate such as "UNK 2007."

Con-med dates should correlate with the dates of the related condition or AE. In particular, the start date should not precede the onset of the condition or AE, and the stop date should not go beyond the end date of the condition or AE. For example, if an infection, such as strep throat, is being treated with antibiotics, the end date of this AE is not when the visible symptoms resolve, but when the infectious agent is eradicated upon completion of the full course of the antibiotic. With conditions, such as Tinea pedis (athlete's foot), with dosage periods that extend beyond the end date of the active infection, enter a separate line that states the intention, i.e., prophylaxis. An example to illustrate this would be as follows:

Entry #1: Lotrimin, T.pedis, application once daily, 1/1/07-1/10/07.

This entry documents the treatment and resolution of a Tinea pedis infection; T. pedis is therefore listed as the indication for the medication.

Entry #2: Lotrimin, T. pedis prophylaxis, application once daily, 1/10/07-2/10/07.

This entry documents the continued use of Lotrimin after the Tinea pedis infection has been resolved, whereby the intent of the continued use is to prevent (prophylax) a subsequent infection.

The **frequency** designates how often a medication is used or taken. There are numerous terms and abbreviations used to describe frequency. Avoid using abbreviations because they can be misinterpreted in unexpected ways. For example, "Q.D" is not a safe abbreviation for once daily because when the "Q" is followed by a sloppy dot, it looks like

"QID." "O.D." is also not a safe abbreviation for once daily, because it is properly interpreted as meaning "right eye." ⁷ Unless the CRF page allows a different mechanism to capture the information, "once daily" should be written out in full to avoid confusion. If the medication frequency changes, create a separate entry on the CRF.

Documenting con-meds that do not have a set frequency, i.e., are taken "prn" (as required), is probably the most common con-med documentation problem. For example, the site may list a prn con-med on the CRF based on the subject's history of use in the medical record even though the subject stopped taking the medication before the study started. Therefore, confirm use of prn medication with the subject. The start date should correspond to the confirmed date the medication was first used or taken during the required reporting period of the study protocol.

Another common problem with prn con-med documentation is for the site to list only a single CRF entry for the prn medication even though it was used multiple, distinct times during the study. This problem often occurs when a study uses a subject diary to capture con-med use. Rather than copy the multiple uses of the medication to the CRF, the site makes a single entry to cover the entire time period of the study, thereby rendering no distinction in the con-med records across the subjects enrolled at that site.

Unless the sponsor specifies otherwise, make a separate entry whenever there is a change in the dosage and/or frequency of the prn medication. Whenever there is a 1-2 week lapse in the taking of the prn medication, make a new entry upon subsequent use of the medication. For example:

Example A: Subject A reported using ibuprofen on October 10, 2005, while enrolled in a study from September 1, 2005 to March 30, 2006.

This usage is commonly reported by study sites as:

Ibuprofen, 200 mg once daily, prn, headache, 2005-continuing.

The correct entry is:

Ibuprofen, 200 mg once daily, prn, headache, 10/10/05-10/10/05.

The first entry is often based on an assumption that the subject is continuing his use of the medication, rather than on the specific dates of use. The second entry documents actual known usage, in this case a single instance.

Example B: Subject A reported using ibuprofen on 10/10/05, 11/13/05, 11/18/05, 12/24/05, and 1/7/06, while enrolled in a study from September 1, 2005 to March 30, 2006:

This usage is commonly reported by study sites as:

Ibuprofen, 200 mg once daily, prn, headache, 2000-continuing.

The correct entry is:

Ibuprofen, 200 mg once daily, prn, headache, 10/10/05-10/10/05.

Ibuprofen, 200 mg once daily, prn, headache, 11/13/05-11/18/05

Ibuprofen, 200 mg once daily, prn, headache, 12/24/05-12/24/05

Ibuprofen, 200 mg once daily, prn, headache, 1/7/06-1/7/06

In the first entry, the single entry of the prn medication may appear to be satisfactory. However, ibuprofen usage during the study period is not accurately portrayed. With this entry, it is impossible to correlate medication with occurrence and severity of medical conditions. In contrast, the second set of entries, albeit more time-consuming, provides useful safety data. Moreover, the data is objective and complements other data that may be subjective.

Conclusion

Accurate and informative con-med documentation makes it much easier to characterize adverse events and drug interactions for a study drug's safety profile. It also minimizes subsequent requests by the sponsor for clarification of study drug name, indication, dosages, and start/stop time periods, potentially a big time saver over the course of a study.

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