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(Tuesday 11:09am) 11 July 2000

Memorandum

To: Center for Clinical Trials faculty and staff

Fr: Curt Meinert

Re: Masking good practice policies and procedures (GPPP)

Definitions

bin number *n* - 1. A **number** (or letter) **code** identifying a storage bin; eg, numbers 1 through 10 identifying bins containing **study drug** or matching **placebo**. 2. A number referenced in a **treatment assignment** identifying the bin from which medicine is to be taken. 3. A number appearing on the label of a medicine dispensed in a **double-masked** trials involving a bin system of drug supply. rt: **bottle number**

blind, **blinded** *adj* - [ME, fr OE; akin to OHG *blint* blind, OE *blandan* to mix] 1. Being without sight; unable to see; having vision measuring less than an amount considered to constitute blindness. 2. Being unable or unwilling to discern. 3. Of or relating to something considered to be the product of stupidity or of ignorance, eg, *blind stupidity*. 4. Being unaware or uninformed of some fact or condition; not recommended usage, use **mask** or **masked**. rt: single-blind, double-blind, triple-blind ***Usage note***: Not recommended for usage in sense of defn 4; see usage note for **mask** for reasons.

blind *n* - 1. Something to hinder sight or keep out light. 2. A place of concealment. 3. Something put forward or done for the purpose of misleading or concealing. 4. **mask** ***Usage note***: Not recommended as a synonym for **mask**; use **mask** rather than **blind** for reasons stated in usage note for **mask**.

blind, **blinded**, **blinding**, **blinds** *v* - 1. To hide or conceal. 2. To **mask** (make **blind**) by withholding, hiding, or concealing some fact. ***Usage note***: Not recommended as a synonym for **mask**; use **mask** rather than **blind** for reasons stated in usage note for **mask**, **masked** *adj*.

collateral unmasking *n* - **Unmasking** occurring as a secondary consequence of an action or event; in regard to **treatment assignment** in **masked trials**, the number of other assignments that are unmasked when the treatment assignment for a single **treatment unit** is unmasked.

complete mask *n* - [**trials**] 1. A **mask** in which all members of a designated **class** or **category** of people associated with a trial (eg, **patients**, **treaters**, **data collectors**, **readers**, or **monitors**) are **masked** to **treatment assignment** and **administration**. 2. A mask in relation to treatment

assignment and administration imposed on patients and all study personnel having patient contact, as in a **double-masked trial**; such a mask applying as well to all personnel responsible for **treatment effects monitoring**, as in a **triple-masked trial**. rt: **nonmask**, **partial mask**, **masking level** ***Usage note***: Masking may be complete for one class of people and partial or none for another. For example, the masking would be complete for patients in a **single-masked trial** and none for **treaters**.

data generation *n* - 1. **data collection** (defn 1) 2. The **generation** of **data** from specimens, documents, or materials collected by others, eg, data generated from blood samples received at a **laboratory** or from readings of fundus photographs made at a **reading center**.

double mask, **double masked** *n* - 1. An arrangement in which two different kinds of persons or groups of persons are **masked**. 2. A **mask** of **treatment assignment** imposed in a **trial** on persons receiving **treatment** and on those administering treatment. rt: **mask**, **single mask**, **triple mask**

double placebo *n* - A **placebo** having two different shapes or forms, eg, a tablet and a capsule, as needed in a **double placebo treatment design**; also double dummy placebo. rt: **single placebo**, **multiple placebo**

double placebo treatment design *n* - A **treatment design** that involves two **placebos**, eg, a **design** in which certain persons in a **trial** receive both placebos or one in which a person assigned to **control treatment** receives one or the other of the two placebos, but not both; also double dummy treatment design. The design arises in **single-masked** or **double-masked trials** that involve two (or more) **test treatments** that cannot be **masked** with a **single placebo** because of differences in the **treatment schedule**, in **dose** or **dosage**, or in route of administration, as in the University Group Diabetes Program. rt: **multiple placebo treatment design**, **single placebo treatment design**

mask, **masked** *adj* - Of, relating to, or being a procedure in a **study**, especially an **experiment** or **trial**, in which a person or class of persons (eg, **patients**, **treaters**, or **readers** in a trial) is not informed of or is denied **access** to information known to or made available to others represented in the study or **experiment**. See **single-mask**, **double-mask**, and **triple-mask** in relation to **treatment assignment** in trials. syn: **blind** (not recommended; see **blind** for reasons) ***Usage note***: Preferred to **blind** because of negative connotations and ambiguities associated with **blind**. **Blind** carries a connotation of mindlessness or stupidity in some everyday usages, eg, *blind luck* or *blind stupidity*. The term **mask** has greater utility across a wider class of trials and settings than **blind** (eg, **blind** can be confusing in vision **trials** with **blind** treatment administration and with blindness as an **outcome measure**) and is a better descriptor of the operational process implied.

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mask *n* - [MF *masque*, fr OIt *maschera*] [general] Something that hides or conceals from view. [**research**] A condition imposed on an individual (or group of individuals) for the purpose of keeping that individual (or group of individuals) from knowing or learning of some condition, fact, or observation, such as **treatment assignment**, as in **single-masked**, **double-masked**, or **triple-masked trials**. syn: **blind** (not recommended usage; see **blind** for reasons) ***Usage note***: See note for **mask**, **masked** *adj*.

mask, **masked**, **masking**, **masks** *v* - To conceal by withholding, hiding, or obscuring some condition, fact, or **observation**. rt: **censor**

masked data analysis *n* - [**trials**] 1. **Data analysis** performed by someone **masked** to **treatment assignment**. 2. Data analyses presented with the **treatment groups** masked.

masked data collection *n* - **Data collection** performed with the imposition of a **mask** in relation to some condition, fact, or **observation**, eg, **disease** status in a **case-control study** or **treatment assignment** in a **clinical trial**. rt: **masked data collector**

masking level *n* - [**trials**] The degree of **masking** employed in a trial in relation to **treatment assignment** for a designated class or category of people (eg, **patients**, **treaters**, **data collectors**, **readers**, **monitors**) associated with the trial; **complete**, **partial**, or none. syn: level of masking ***Usage note***: The level may range from complete to none, for different classes or categories of people, depending on the design and operating features of the trial. For example, it is by definition complete for patients, treaters, and monitors in a triple-masked trial and usually complete for data collectors and readers. It may be complete for one class and partial or none for other classes of people, eg, as would be the case in a nonmasked trial involving masking of some of the data collectors and masked **treatment effects monitoring**.

medication identification number, **medication Id number**, **medication Id** *n* - A number or set of alphabetic characters or symbols, that, when decoded, serves to identify a medication being dispensed and administered in double-masked fashion, eg, **patient identification number** or **bin number**.

multiple placebo *n* - [**trials**] A **placebo** that has two or more forms or shapes in a given trial, eg, as required for **masking** in a trial involving two or more **test treatments** having different forms or routes of administration. rt: **single placebo**, **double placebo**

multiple placebo treatment design *n* - A **treatment design** that involves two or more **placebos**, eg, as needed in a **drug trial** having two or more **test treatments**, each requiring its own **matching placebo**, eg, as used in the University Group Diabetes Program for masking tolbutamide and phenformin. rt: **multiple placebo**, **single placebo treatment design**

partial mask *n* - [**trials**] 1. A condition in which only some members of a designated class or category of people associated with a trial (eg, **patients**, **treaters**, **data collectors**, **readers**, or **monitors**) are **masked** to **treatment assignment** and **administration**. 2. The state of being **partially masked**. 3. A **mask** that is not **complete** in the sense of defns 1 or 2 of **complete mask**. 4. A **double mask** in which a specified subset of people are not masked, eg, the subset responsible for changing **dosages** of the assigned treatment over the course of the trial. 5. A double mask that is complete from one perspective but not from another; a mask in a trial with two or more pairs of **test** and **control treatments** in which the treatments in a given pair are masked one to the other, but not with respect to all other pairs, eg, an asthma trial with a **parallel treatment design** involving two or more test-control pairs of treatments in which all test and control treatments are to be administered via nasal inhalation and in which the two treatments represented by any given pair are to be dispensed from identical canisters, but in which the shape, form, or size of such canisters (and perhaps the required number of inhalations from them) for one such pair of treatments is different from that for another such pair. rt: **complete mask**, **nonmask**, **masking level**

single masked, **single mask** *n* - [**trials**] 1. A condition in which those being treated are **masked** in regard to treatment but those applying the treatment are not. 2. A condition in which either those being treated or those applying the treatment (but not both) are masked in regard to treatment. 3. A condition in which only one class of people (eg, **patients**, **treaters**, or **readers**) is masked in regard to treatment. ***Usage note***: See **single-mask** *adj*.

triple mask, **triple masked** *n* - [**trials**] An arrangement involving a **double mask** plus masking for the individual (or group of individuals) responsible for **treatment effects monitoring**.

P&P 1: When designing a trial, strive for the highest level of treatment masking consistent with safety and practicality.

1. Opt for double masking where safe and practical.
2. Default to single masking where it is safe and practical to withhold assignment from patient or treater, but not from both.
3. Opt for partial masking if full masking is not possible.
4. Opt for unmasked administration if masking is considered unsafe or impractical.

Comment

Generally, in regard to treatment administration, data collection, and generation, some masking is regarded as better than none at all. Hence, the impact of the P&P is to remain as high up the hierarchy of options as is safe and practical.

P&P 2: In unmasked trials or single-masked trials, vest treatment and data collection responsibilities in different persons if such separation is feasible, practical, and necessary.

Comment

Separation of the two functions allows the trialist to create a self-imposed mask on data collectors, such as in the HPT. The separation has potential to reduce the risk of treatment-

related bias in the data collection process. However, the separation has logistical implications and should not be imposed if it is unlikely to be effective or useful (eg, in trials involving "hard" outcome measures) or where the risk of treatment-related feedback bias is low.

P&P 3: Mask persons responsible for generating data where possible.

Comment

Even if treatments cannot be masked, it is usually possible to mask data generators when generation takes place remote from the clinic, eg, as with most laboratory determinations and central readings.

P&P 4: Do not mask treatment if the masking carries non-negligible risk for patients.

Comment

The use of invasive procedures for masking is generally not justified unless it can be argued that the risk of harm or misadventure is nil (eg, as may be the case with placebos administered by injection).

P&P 5: Do not mask treaters if treatment assignment must be known for the proper or safe care of a person.

Comment

The impact of the P&P is to largely preclude masking in trials requiring titration of dosage (except, perhaps, where it can be done by separation of function).

P&P 6: Do not maintain a mask if unmasked information is needed for the care or ensuring the well-being of a person.

Comment

The impact of the P&P is to require the trialist to establish procedures to unmask treatment assignment if the information is needed to care for a patient or someone else (eg, the child of a patient who has taken an unknown quantity of the patient's study medication).

P&P 7: Do not mask if masking is a charade.

Comment

It is likely to be a charade if treatments produce telltale signs with high probability.

P&P 8: Do not mask at the expense of informed competency.

Comment

Assume masking reduces competency if it can be argued that treatments must be known to properly care for persons enrolled in a trial or to make informed decisions in regard to TEM. See memo of 26 April 2000 from CLM.

P&P 9: Do not mask treatment if masking carries risk of error or misadventure.

P&P 10: Do not mask the treatment effects monitoring committee.

Comment
See memo of 26 April 2000 from CLM.

P&P 11: Where possible, collect information on the quality of masking at the conclusion of the trial.
Comment
Typically, done by asking patients and study investigators to make their best guess as to treatment assignment.

P&P 12: Establish procedures to preserve the masking.
Comment
Typically achieved by stopping treatment (without revealing the identity of the treatment) if a patient presents with signs or symptoms believed to be treatment-related or who develops conditions where continued treatment is questionable or contraindicated.

P&P 13: Construct masking which is consistent with approved formulations and routes of administration.
Comment
Generally, it is best to construct masking so as to be able to dispense product as produced by the manufacturer. Usually, any change (eg, placing tablets in capsules to mask appearance to avoid use of multiple placebos) raises questions regarding the bioavailability of the repackaged or reformulated product.

P&P 14: Construct masking schemes which minimize the risk of collateral unmasking.
Comment
The chance of collateral unmasking is eliminated if, the coding of treatment assignments is unique (eg, as in schemes where treatment assignment is tied to patient identification number). However, unique systems of labelling are more expensive to set up and maintain and, generally, waste more drug than is the case with bin systems of supply. The amount and cost of wastage can be considerable, especially in trials involving expensive drugs, a long course of treatment, and in which the entire supply of drug needed to treat a person is shipped when the person is randomized.

The risk of collateral unmasking in bin systems of supply is a function of the number of persons receiving medication from the same bin. In such systems, unmasking treatment for a person receiving medication from bin X is tantamount to unmasking the assignment for all persons receiving medication from bin X.

The amount of collateral unmasking that occurs is a function of the number of bins used for dispensing medications and the number of persons randomized at a clinic. The potential for collateral unmasking diminishes as the number of bins increases. Generally, the risk of collateral

unmasking is considered to be acceptable if the ratio of the number of persons to be randomized in a clinic to medication bins is ≤6.