4G CLINICAL

Protecting the Blind

Knowledge Sharing Series

Protecting the Blind

Introduction

Since protecting the blind is the top priority in any blinded study, accidentally breaking this blind is one of the Big Four 'We Will Never' Mantras at 4G Clinical.

Revealing the treatment arm of a patient or the kit type of an assigned kit will directly unblind a patient. Thus, a full unblinding incident will result in a costly loss of patient data which cannot be incorporated as intended. Luckily, RTSM systems, such as Prancer RTSM™, have safeguards in place to prevent full unblinding from harming the data.

However, partial unblinding can be equally as damaging to the data integrity of a study. This is the case especially if information from several partial unblinding events can be "accumulating over time. While there is no surefire way to prevent unblinding, advanced clinical software can help mitigate the impact of this in trials. In this white paper we explore some of the ways that accidental unblinding can occur, including partial unblinding, and how the 4G solutions are designed to avoid these risks.

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Reports

Many summary reports include aggregated data such as in an inventory summary report listing the number of kits in each status at a site. The unblinded version of this report would have a row per kit type detailing the unblinded kit identifier. The blinded version of this report would replace the kit type with a blinded kit identifier. However, it is important that the data is aggregated using the blinded identifier and not still using the unblinded one. Although not directly unblinding, it is clear that there is more than one kit type at the site if more than one row is listed with the same blinded identifier. Blinded lot numbers and expiry dates are also common areas where incorrect aggregation could lead to partial unblinding. Therefore, aggregation must be performed based on the data displayed to the user which may be different for blinded and unblinded versions of the same report.

Protecting the Blind

It is now common for users to attend virtual meetings and share their screens. These meetings may have a mix of blinded and unblinded users in attendance. An unblinded user may be sharing their screen and viewing a blinded summary report, however on 'drilling down' to the detail report the unblinded version of this report is displayed therefore unblinding the blinded users in attendance. It is important for the system to clearly identify blinded and unblinded versions of reports but also for it to prevent the drill down from a blinded report to directly show an unblinded one. In Prancer RTSM™, upon selecting a blinded report, a user is 'locked' into blinded mode and any drill down takes the user to the blinded report. They must specifically select to view the unblinded report or switch out of blinded mode. This minimises the risk of accidentally screen sharing an unblinded report.

Inventory summary for an unblinded user

Site	*Kit Type*	*Available*	*Damaged*	*Lost*
1001	Active	2	0	1
1001	Placebo	0	2	0

Inventory summary for a blinded user – incorrect aggregation revealing split of kit types

Site	*Kit Type*	*Available*	*Damaged*	*Lost*
1001	Active or Placebo 10mg	2	0	1
1001	Active or Placebo 10mg	0	2	0

Inventory summary for a blinded user – correct aggregation

Site	*Kit Type*	*Available*	*Damaged*	*Lost*
1001	Active or Placebo 10mg	2	2	1

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Unblinded Pharmacist Designs

The unblinded pharmacist study design, one of the most challenging models when it comes to maintaining the blind, comes with its own risks. Primarily, the sharing of any information about patient visits can result in unblinding. A typical design may have a locally sourced placebo or comparator and active IMP, which is managed and assigned by the RTSM. Therefore, active patients will have kits assigned but placebo ones won't. This makes any assignment information or even the mention of a patient being assigned kits unblinding. Other common actions on the patient can also be unblinding in this design. For example, only active patients will have kit replacement visits, and so knowing that a patient has had a kit replaced unblinds them.

In Prancer RTSM™, assignments can be flagged as hidden and won't appear to blinded users. Also, unscheduled visits such as kit replacement can be flagged as unblinding, and no record of these having occurred will be displayed to a blinded user. This ensures that patients will not have access to information that could compromise the data integrity.

Assignment (Dispensing)

Low inventory levels in a blinded study can lead to partial unblinding. If there is a stockout for one patient but you then successfully assign for another without receiving a shipment, then you know that they required different kits and are therefore on different arms or dose levels. The system used for supply management should be able to check that there is sufficient inventory for all treatment arms before proceeding with assignment. This is most common at the randomization visit, where this will be blocked unless there is sufficient inventory to randomise a patient to all open arms. It is also a risk at subsequent visits however where there needs to be consideration given to preventing a patient from receiving an assignment when there are sufficient kits for their arm but not for all arms. There is a trade-off between protecting the blind and avoiding a patient not being able to receive their assignment; most sponsors therefore only implement this check at the randomization visit.

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When more than one kit type is assigned at a visit, it is important to consider what order the kit numbers are displayed in on the screen and on notifications. If kits are sorted by kit type and then kit number, it may be possible to identify the quantity of each kit type assigned due to kit number separation, even if the kit numbers are blinded across kit types. In the following example, two distinct kit number ranges appear on the chart below. This may not be obvious when a single assignment is displayed. However, when several assignments are shown together, a pattern appears. We don't know the actual kit types assigned, but we could discern that the assignments are for different dose levels. This compromises the blind and should be avoided.

Assignment 1	*Assignment 2*	*Assignment 3*
2348	*4126*	*2674*
6247	*6289*	*2914*
9247	*2458*	*3258*
9962	*2514*	*6195*
5416	*6514*	*7425*
7483	*8137*	*9455*

Prancer RTSM™ offers several kit selection orders within the expiry date order, including by kit number, kit sequence number, or random. The display of kit numbers on the screen and notification however is always ordered by kit number across all kits assigned at a visit. This ensures that no pattern can be determined from the list of kits assigned.

Lot Blinding

Lots may require several different identifiers, including blinded, unblinded, depot lot IDs, and expiry dates. Having the required identifiers available in the system is key to ensuring that the lots can be created as required and that the relevant IDs are displayed to the correct user roles. If the system does not provide sufficient IDs, then users may incorrectly use the IDs available, leading to an unblinding scenario.
Prancer RTSM™ provides a blinded and unblinded lot identifier as well as a lot-level depot lot number. It also provides unblinded kit type lot and depot lot identifiers. These are clearly labelled on the lot creation screen as to whether they display to blinded or unblinded users to mitigate any unblinding risk.

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For blinded kit types, single kit type lots have the risk of being partially unblinded. The blinded lot identifiers must be kept identical between lots containing the blinded kit types. It is therefore much safer for blinded kit types to always be contained in lots with the other kits in the blinding group. This ensures that the blinded lot identifiers stay consistent across kit types. Prancer RTSM™ can be configured to prevent the creation of lots containing a single blinded kit type or provide a clear warning message should a user create one.

Shipment blinding

It is standard practice to select kits for a shipment in the sequence number order. This is required by depots to ensure efficient picking of kits. Depots will need to receive an order file and/or notification with kits in sequence number order. However, as sequence number is unblinding, this results in the order being partially unblinded due to pack separation. Any shipment notification sent to blinded site users must therefore not be ordered by sequence number and must instead be ordered by kit number.

'Single' Kit Shipments

Minimizing drug wastage is an ever-increasing priority in clinical trial supply management. Having the right kits available at the right time for every patient without having large stocks on site which might expire prior to assignment is the aim. However, the drive to minimize wastage can lead to partial unblinding risks. Sending small and frequent shipments to a site can easily reveal patterns in which kits a patient receives and which they don't. This can partially unblind patients, as you can identify that they are on different arms. For example, a patient receives two kits at their visit, and a few days later a shipment arrives with two kits. It is easy to deduce that those two kits are the same type as the ones the patient just received. Tracking who they are assigned to allows a pattern in arm assignment to be deduced.

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One common solution to this is adding one or more extra kits to a shipment. Unfortunately, the extra kits aren't needed and may never be needed at the site which increases wastage. Being intelligent about the kit types added to blind the shipment reduces the risk of wastage. Adding a kit type that is relevant ensures the blind is maintained and minimizes wastage. Prancer RTSM™ offers several different options to determine when a shipment requires blinding and how to determine the most suitable kit type to blind the shipment with whilst keeping an element of randomness. The same rules can also be applied to manual shipments with either a soft or hard check of the rules, or the shipment can be blinded automatically.

Pack separation

When designing your kit lists, do you consider how you might extend them, or add new blinded kit types in the future if needed? With adaptive study designs becoming more prevalent, it increases the chances that you will need extra kits either because you are increasing the number of patients or lengthening the visit schedule. You may also need to add a new blinded kit type to accommodate a new dosing schedule.

Original kit list generated with 3 kit types in ratio 1:1:1 and 1000 kit numbers in the range 1000-1999.

Kit Number	*Kit Type*
1925	Active 10mg
1148	Placebo
1091	Active 20mg

Later in the study, a new Active 40 mg kit type is added, but the existing kit number range is full, and so a new kit number range must be used. Creating this with just the one kit type in a distinct range is fully unblinding. As a solution, the best option in this scenario is to generate a new kit list with all 4 kit types but only to use the numbers for the 40 mg kit type.

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A better way to manage this is to preempt the need for an additional kit type and use a wider kit number range initially. 4G's Ultima Rand allows a superset, kit number range to be defined and kit lists to be generated from within that range. Kit numbers are randomly taken from those available in the superset thus ensuring that if a new kit list is generated in the future, there is no separation of kit numbers.

Summary

The aforementioned insights call attention to the unexpected ways in which the blind could be unintentionally broken in a study. When designing your next RTSM study, these risks can serve as a guide to ask your vendor how they protect the blind in the scenarios you might encounter.

Every study is unique, and there is no substitute for having an experienced team designing your RTSM implementation. 4G has a wealth of highly experienced staff, many having worked in the industry for over 20 years. Having this expertise on your study from Day 1 helps to avoid the potential pitfalls of partial unblinding and ensures that your study runs without any problems.

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Meet the **Author**

Jon Sendell is a seasoned Product Manager with over 20 years of experience in clinical trial technology. His expertise spans RTSM/IRT, EDC, CTMS, and clinical data management. From hands-on coding to leading international teams, Jon has driven the development of configurable RTSM systems and managed vendor onboarding. With a BSc in Physics from the University of Birmingham, he combines analytical rigor with practical expertise to support efficient, risk-aware clinical trial operations.

For more details on how 4G Clinical can assist you visit **4gclinical.com**

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About us

4G Clinical's suite of innovative RTSM and clinical supply optimization software provides the right-sized support for any phase or trial complexity. At 4G Clinical, all studies are supported by a team of RTSM experts to advise trial teams on the best path forward. Our operations team distinguishes itself through their extensive industry expertise and deep understanding of trial designs and mid-study adjustments. As a critical partner throughout clinical development, we can help you seamlessly transition and scale your trials through both protocol and supply complexities to help **bring crucial medicines to those who need them, *faster.***