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Supplementary Information 3.

VICI Trial IMP management database.

To optimise the management and accountability of the IMP we designed a secure internet-based IMP management system (“IMP database”). The IMP database allows local research teams to manage IMP bottle allocation whilst remaining masked to the participants’ allocation. Figures A and B show the flow of IMP bottles from the pharmacy and research team perspectives, respectively.

Role-restriction

Local site pharmacists and research teams, the manufacturing pharmacy and CTEU Bristol can remotely manage IMP accountability without the requirement for paper records or on-site monitoring visits (unless triggered following accountability issues identified from centralised monitoring of reports from the IMP database), which has greatly reduced the resources required to manage the trial. Role-restricted database access means each user-type utilises a single database system but are only able to perform tasks required for their role. For example, the manufacturing pharmacy has access to the functions required to process orders of stock but do not have access to any other functions. The IMP database has streamlined processes for IMP accountability and reduced potential for errors. It crucially prevents unmasking by personnel who are not permitted to do so.

Database interactivity

The IMP management database interacts directly with the main trial database (which incorporates the randomisation system). This interaction allows the IMP database to a) calculate the amount of IMP stock that is required locally based on the number of participants randomised at sites and b) automatically calculate the type (i.e. 25 mg or 50 mg dose) and number of bottles of IMP that should be allocated to a participant based on the visit stage using the baseline and follow-up data visit data. One caveat is that, if previous visit data entry is not up-to-date, the IMP database could automatically detect the incorrect visit stage and allocate too few or too many bottles for that time-

point. To minimise this risk, a member of the local research team can manually specify the most recent time-point.

Automated notifications

The IMP database is programmed to send email notifications automatically. The notification emails are either triggered alerts or confirmation of actions. Local site pharmacists and the CTEU Bristol receive alert notifications of low stock, prompting local pharmacists to place orders for additional stock. Alert notifications are also triggered when IMP is due to expire within 92 days. Such alert notifications include an Excel attachment with a list of all affected bottle numbers. Confirmation of action notifications are copied to local site pharmacists, local users (i.e. the user who performed the action) and the CTEU Bristol when bottles of IMP are allocated, confirmed as dispensed or when the bottle allocation is cancelled prior to dispensing. Upon placing an order for stock, the local site pharmacists, manufacturing pharmacy and CTEU Bristol receive a notification with an Excel attachment detailing the contents of the order. The automated alert and confirmation emails enable the trial manager to track activity and identify and resolve issues promptly even when not logged in to the IMP database.

IMP distribution

The IMP database facilitates stock distribution between manufacturing pharmacy and sites. The database enables a) standard ordering where stock is dispatched by the manufacturing pharmacy and delivered to sites and b) re-distribution of stock from one site to another, via the manufacturing pharmacy. Redistribution of stock has been necessary in the VICI trial because a) the cost of the IMP limited the amount that could be manufactured, b) there are 22 sites and c) each site was expected to recruit few participants (< 10). Sufficient 25 mg IMP was manufactured to supply each participant with one bottle at baseline and for approximately half of participants to restart treatment following disease recurrence. In the late stages of recruitment all 25 mg IMP stock was distributed to sites, leaving no 25 mg IMP stock at the manufacturing pharmacy. In circumstances where a site needs to

either randomise or re-start a participants' treatment yet does not have sufficient 25 mg IMP in stock to do so and there is no stock at the manufacturing pharmacy, CTEU Bristol assists with re-distribution of stock. The IMP is re-distributed as follows, with each action completed via the IMP database:

- a) CTEU Bristol locates an appropriate bottle at a different site (Site A) to that which requires it (Site B).
- b) CTEU Bristol places a custom-order for the bottle to be collected from site A and delivered to the manufacturing pharmacy.
- c) Site A logs dispatch of the order.
- d) The manufacturing pharmacy logs receipt of the order.
- e) CTEU Bristol places a custom-order for the bottle to be collected from the manufacturing pharmacy and delivered to Site B.
- f) Manufacturing pharmacy logs dispatch of the order.
- g) Site B logs receipt of the order.
- h) The bottle is available to allocate and dispense at Site B.

The IMP is re-distributed via the manufacturing pharmacy so as quality assurance checks can be completed prior to dispatching to another site.

Figure A. Flow diagram of the IMP bottle pathway from the pharmacy perspective

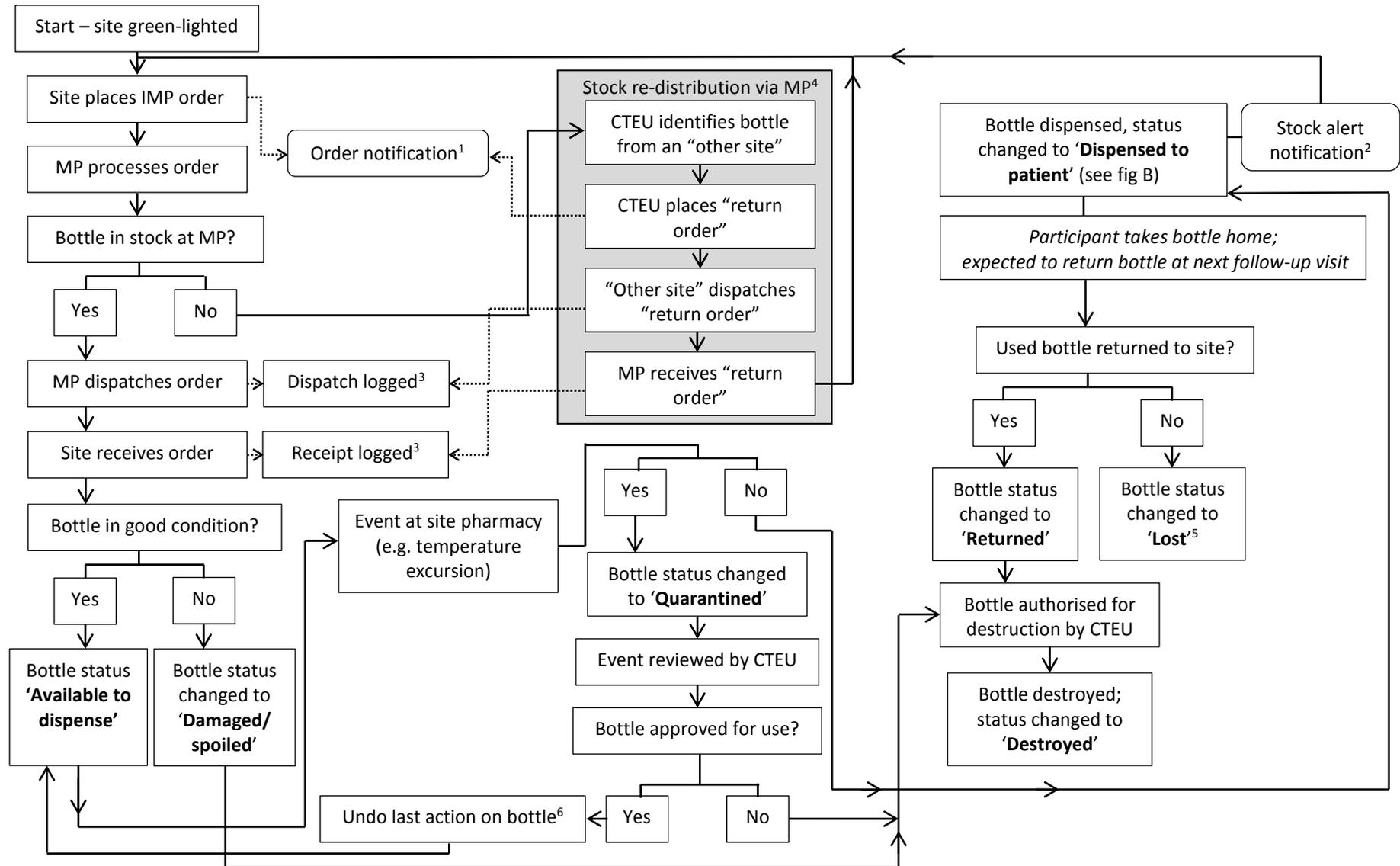


Figure A Footnotes

MP = manufacturing pharmacy

¹ An email notification containing the order details is sent to the MP, site pharmacy user and CTEU Bristol.

² An email notification of the stock alert is sent to all pharmacy users at a site to prompt action, and CTEU Bristol for reference.

³ Dispatch and receipt actions are logged to reconcile the status of the IMP with the IMP database. Orders can only be logged as received after they have been logged as dispatched. Failure to log the change in status of the order at the appropriate steps prevents the bottles from being made available to dispense.

⁴ The stock re-distribution via MP pathway describes the process for ordering stock from a site and returning it to the MP (“return order”), where it can then be ordered by another site. This is performed under circumstances where stock is not available at the MP but appropriate bottles are available at other sites. See ‘*IMP distribution*’ section above for details.

⁵ Bottles are only logged as ‘lost’ once the site has confirmed with the participant that the bottle has been discarded. If the participant forgot to return the bottle at the required time-point they return can them at a later follow-up visit.

⁶ Undoing the last action on a bottle will revert the bottle status from ‘quarantined’ to the status held previously, e.g. available to dispense.

Figure B. Flow diagram of IMP bottle pathway from the research team perspective

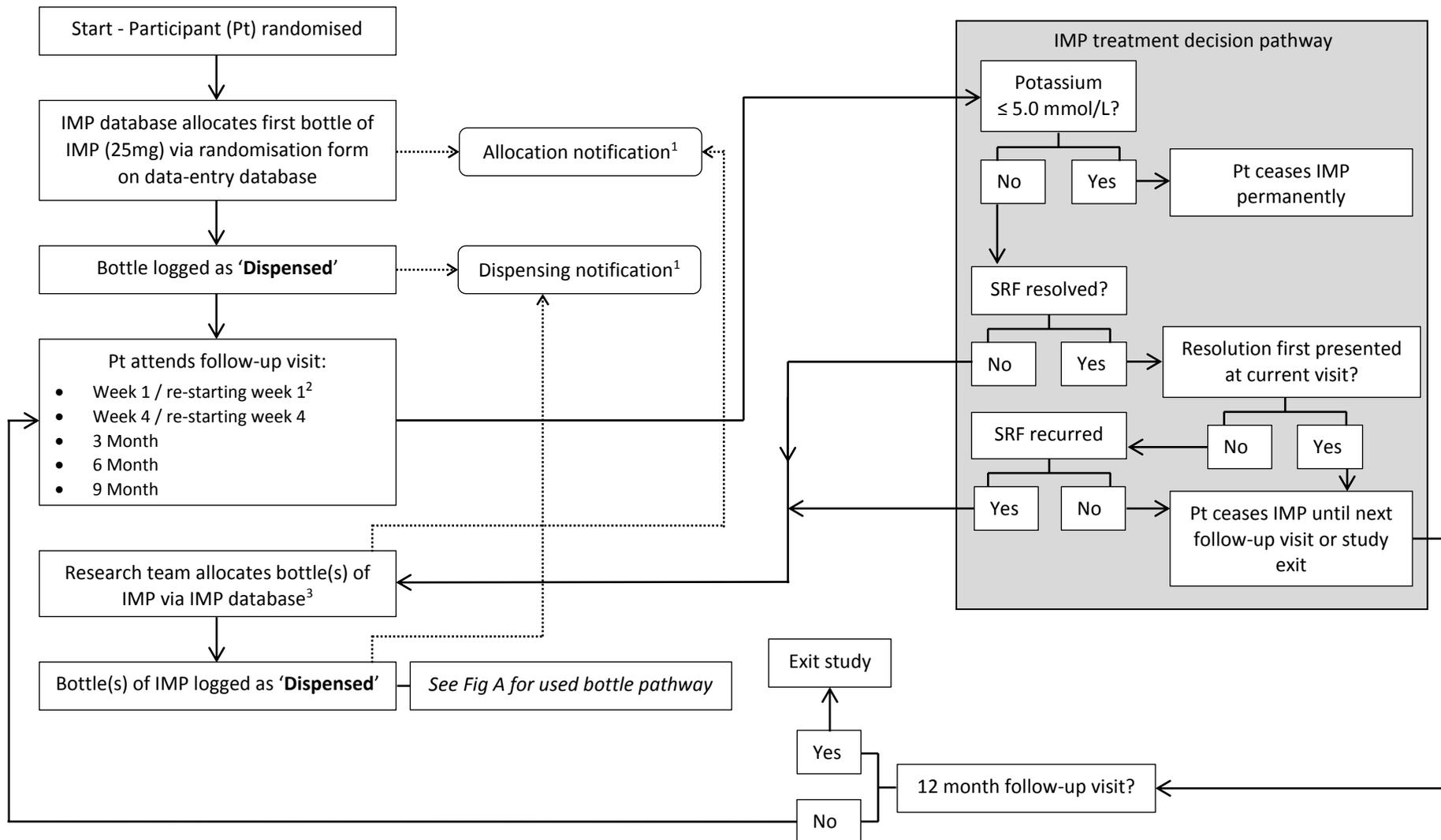


Figure B Footnotes

SRF = subretinal fluid

¹ The allocation and dispensing notifications are passive checks that enable site users and CTEU Bristol to track actions. The notifications contain the bottle number(s) which have been allocated or dispensed. Site pharmacists use the allocation notification to confirm the bottle numbers recorded on the paper copy of the prescription.

² At week 1 and re-starting week 1 there is no assessment of SRF.

³ 1 bottle of 25 mg IMP allocated for re-starting IMP due to recurrence of SRF; 1 bottle of 50 mg IMP allocated at week 1 and re-starting week 1; 2 bottles of 50 mg IMP allocated at week 4 and re-starting week 4; 3 bottles of 50 mg IMP allocated at 3, 6 and 9 months.