Patients in clinical trials are sub-optimally protected for drug–drug interactions: a call for action

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Patients in Clinical Trials are Sub-Optimally Protected for Drug–Drug Interactions: A Call for Action

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It is essential that patients in clinical trials of investigational medicinal products are protected from harm. However, some of the advances made to improve medication safety in routine clinical care have only sparsely trickled down to clinical trials. For instance, in routine care, drug–drug interaction data from the approved product information[1,2] is incorporated in prescribing and dispensing software to generate an automatic alert when a drug–drug interaction may occur. In contrast, drug–drug interaction management with investigational medicinal products is performed manually by the study physician or pharmacist based on instructions in the study protocol.

In our experience, instructions for drug–drug interaction management in clinical studies with unlicensed investigational medicinal products are highly variable, often outdated, and/or incomplete. To our knowledge, this problem has not yet been investigated in a systematic manner. We decided to focus on investigational medicinal products with CYP3A-related drug–drug interaction management.

Between January 1, 2022, and March 1, 2023 we reviewed phase 2/3 study protocols of ongoing clinical trials in adults with unlicensed investigational medicinal products being small molecules, supported by the Pharmacy at RadboudUMC, Nijmegen, the Netherlands. Unlicensed investigational medicinal products not being small molecules (i.e., large proteins and antibodies) are usually not (or minimally) susceptible to drug interactions and were therefore not part of this investigation. Investigational medicinal products that were already licensed for other indications were also excluded.

For each unlicensed investigational medicinal product, we recorded the clinical development phase, the drug–drug interaction profile of the product known at the time of writing the study protocol (substrate/inhibitor/inducer), the list of prohibited medications when mentioned, and the relevant sources that were described. The unlicensed investigational medicinal product name/number and name of sponsor were not recorded in order to guarantee confidentiality.

In order to facilitate the analysis and interpretation of the data, we decided to focus on unlicensed orally administered investigational medicinal products with CYP3A-related drug–drug interaction management (n = 12) as this was by far the largest group of medications where drug–drug interaction management was described.

The 12 unlicensed investigational medicinal products were equally divided between clinical development phases 2 and 3. All were multinational studies. These included nine CYP3A substrates, three CYP3A inhibitors, and two CYP3A inducers.

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This study has previously been presented at the annual American College of Clinical Pharmacology meeting, Bellevue, WA, USA on September 10–12, 2023 (abstract #134)

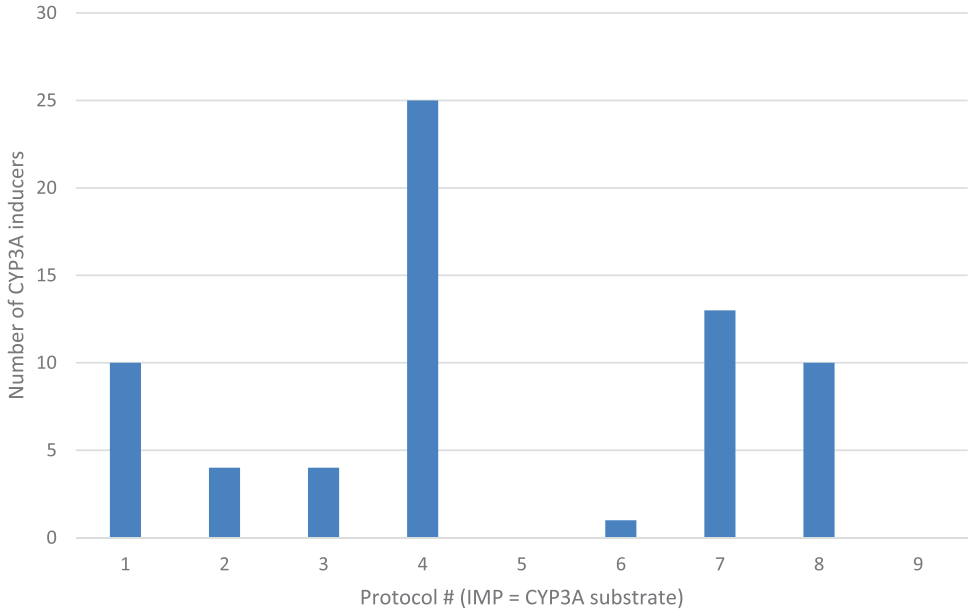

Figure 1. Distribution of number of CYP3A inducers mentioned in the nine study protocols with an unlicensed investigational medicinal product (IMP) that is a CYP3A substrate. For a detailed list of these CYP3A inducers, see Table S1.

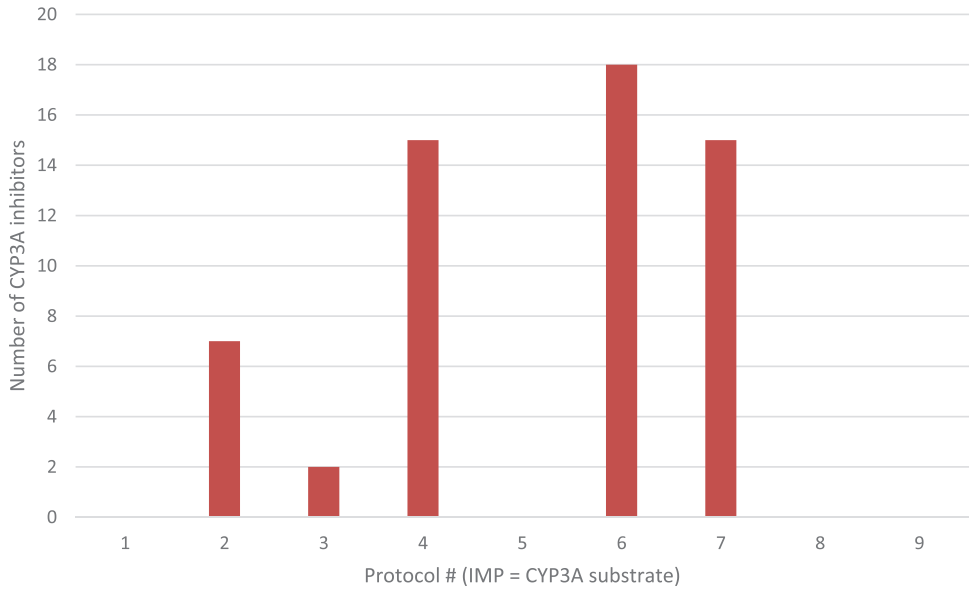

Figure 2. Distribution of number of CYP3A inhibitors mentioned in the nine study protocols with an unlicensed investigational medicinal product (IMP) that is a CYP3A substrate. For a detailed list of these CYP3A inhibitors, see Table S2.

Figure 1 shows the number of CYP3A inducers that were listed as prohibited co-medication in case the unlicensed investigational medicinal product was a CYP3A substrate (nine study protocols). This number varied between 0 and 26 agents per protocol, with the highest reference to rifampicin (n = 6), carbamazepine (n = 6), and St. John's wort (n = 5). Table S1 lists all CYP3A inducers described in these nine study protocols.

For CYP3A inhibitors this varied in the same nine study protocols between 0 and 18 agents, with the highest reference to clarithromycin, ketoconazole, and telithromycin (all n = 4) (see also Figure 2 and Table S2). Remarkably, some agents that are withdrawn from the market (e.g., boceprevir, telaprevir, and nelfinavir) were still listed as prohibited CYP3A inhibitors. Grapefruit juice was only mentioned in four of the nine study protocols with a CYP3A substrate

The number of prohibited CYP3A substrates in case the unlicensed investigational medicinal product was a CYP3A inhibitor (three study protocols)

or a CYP3A inducer (two study protocols) varied between 0 and 74 agents (Table S3). In one study protocol, reference to the FDA website with CYP3A substrates/inhibitor/inducers was made. One study protocol warned that "sensitive CYP3A substrates with narrow therapeutic index" were not allowed without further specification which agents fulfill that definition. In two study protocols a reference was made to documents in the Investigator Site File which were not present in the Pharmacy.

The clinical development phase did not appear to be related to the (in)completeness of drug–drug interaction management instructions.

Although we acknowledge that drug–drug interaction management during clinical development of a drug can be challenging, the lack of (any) consistency that we observed in the study protocols is worrisome, and potentially harmful to study participants. Reference to specific CYP3A substrates, inhibitors, or inducers appears to be highly variable and/or accidental.

Inadequate drug–drug interaction management may not only harm study participants, but it may also influence the clinical evaluation of the unlicensed investigational medicinal product by leading to adverse events or loss of efficacy. Drug–drug interactions also increase the variability in efficacy and safety between subjects. In the end, this could negatively affect the clinical development of a new drug.

In 2007, Van Spall et al. reported in a series of 283 clinical trials published between 1994 and 2006, that 54.1% of these trials had at least one concomitant medication listed as an exclusion criterion.[3] More recently. Marcath et al. have analyzed drug–drug interaction management retrospectively in two completed oral chemotherapy trials conducted by SWOG Cancer Research Network.[4] At enrolment, 31 of the 167 participants (18.6%) had a drug–drug interaction, of whom 20 (12.0%) was a protocol violation so the patients should have been excluded. During follow-up, another 16 patients (9.6%) had a co-medication added that caused a drug–drug interaction, of which 14 (8.4%) violated exclusion criteria. Thus, the problem of inadequate drug-drug interaction management in clinical trials is not negligible.

We can think of multiple explanations for the inconsistency and incompleteness of drug–drug interaction instructions in clinical trials. First, during clinical development of an agent its drug–drug interaction profile is still under investigation, and it might be challenging to provide accurate instructions for drug–drug interaction management. While this certainly will be true in earlier phases of clinical drug development (phase 1/2), this is likely to be incorrect during phase 3. Our analysis did not show any difference regarding incompleteness of drug–drug interaction instructions of unlicensed investigational medicinal products in phase 2 or 3.

Second, we acknowledge that not all CYP3A substrates are the same, and differential drug–drug interaction management makes sense when combined with CYP3A inducers or inhibitors. Similarly, investigational drugs may have variable effects on CYP3A induction or inhibition, which may impact the number of prohibited CYP3A substrates. Our analysis, however, shows that even for comparable CYP3A substrates the list of strong CYP3A inducers (expected to cause $\geq$80% reduction in AUC) or strong CYP3A inhibitors (expected to cause a $\geq$5-fold increase in AUC) is still highly variable. Thus, differential sensitivity to a CYP3A-mediated drug interaction does not appear to fully explain this variability.

Finally, it does not come as a surprise when one realizes that drug–drug interaction information for *licensed* medication described in approved product information documents is *also* incomplete, as we have demonstrated repeatedly in a number of commentaries.[5,6] There is, however, an important difference here as patients who are prescribed a licensed medication are being protected by automated clinical decision systems that contain warnings for extended lists of co-medications that can be involved in a drug–drug interaction. And while these systems may also be inconsistent and incomplete, as we have shown previously,[7] this at least guarantees some degree of patient safety when taking multiple medications. Such a safeguard is absent when patients participate in clinical trials.

This latter observation may also open the door to potential solutions for this—in our opinion—sub-optimal protection of study participants from the occurrence of drug–drug interactions when participating in a clinical trial. Based on the known drug interaction profile of an unlicensed investigational medicinal product, clinical pharmacologists should be able to extrapolate this to a larger set of potential co-medications that are either prohibited or require additional interventions. Such an approach was recently described by Fletcher et al. for the investigational Covid-19 agent ensitrelvir.[8] A similar approach is used by us in the MISSION study using our www.DDIManagers.com platform.

Based on our observations in this study and the few examples elsewhere we call for action among all stakeholders (pharma companies, regulatory authorities, ethics committees, funders, academia, and clinicians) to develop guidance and best practices for improved drug–drug interaction management of participants in trials to improve the benefit–risk ratio of investigational medicinal products.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.