PREemptive pharmacogenomic testing for Preventing Adverse drug REactions

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To determine whether implementing pre-emptive PGx testing of an entire panel of clinically relevant PGx markers, to guide the dose and drug selection for over 39 commonly prescribed drugs, will result in an overall reduction in the number of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON50620

Source
ToetsingOnline

Brief title
PREPARE

Condition

- Other condition

Synonym
Adverse drug reactions

Health condition

bijwerkingen

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Horizon 2020

Intervention

Keyword: Adverse drug reactions, Pharmacogenetics, Pharmacogenomics, Preemptive

Outcome measures

Primary outcome

The primary endpoint of PREPARE is a composite endpoint of clinically relevant drug-genotype associated ADRs.

Secondary outcome

Secondary outcomes include other clinical outcome measures (e.g. total number of ADEs, dose changes, drug cessations etc.), a cost-effectiveness evaluation, and process metrics for implementation; the latter includes physician and pharmacist adherence to the DPWG guidelines, and the acceptance of PGx-informed prescribing to health care professionals and patients.

Study description

Background summary

In recent years, multiple randomized controlled trials for a variety of drug-gene combinations have strongly indicated that pharmacogenomics (PGx) testing prior to prescribing, to guide the dose and drug selection, can improve patient outcomes. Almost 15% of medicinal products evaluated by the European Medicines Agency between 1995 and 2014 contain PGx information in their product label. PGx-guided therapeutic dose and drug selection recommendations have also been created and published by the Dutch Pharmacogenetics Working Group (DPWG). However, despite these major scientific and clinical advances in PGx, and the availability of several commercially available PGx tests, the application of PGx into routine care remains very limited. PREPARE will implement pre-emptive genotyping of an entire panel of clinically relevant PGx markers (for which

DPWG guidelines are available: *pharmacogenes*) across seven countries within the European Union, in a prospective clinical study and investigate its collective impact on patient outcomes and cost-effectiveness.

Study objective

To determine whether implementing pre-emptive PGx testing of an entire panel of clinically relevant PGx markers, to guide the dose and drug selection for over 39 commonly prescribed drugs, will result in an overall reduction in the number of clinically relevant drug-genotype associated adverse drug reactions (ADRs). We hypothesize that the implementation of PGx-guided drug prescribing will reduce both the occurrence and severity of drug-genotype associated ADRs in comparison to patients receiving standard of care treatment.

Study design

A multi-center, open, randomized, cross-over implementation study conducted in seven countries across Europe. Countries will be randomised to start with either PGx-guided prescribing (study arm) or standard of care (control arm). After this period, a new set of patients will be recruited and the opposite strategy will implemented. All study patients will be followed-up for a minimum of 12 weeks; maximum follow-up is limited to 22 months per patient. Intervention: All patients will donate a DNA sample that will be genotyped for a panel of 48 genetic variants in 13 pharmacogenes. For patients within the study arm, their results will be: 1) recorded in the (electronic) medical record and 2) provided to the patient in the form of plastic card, akin to a credit card. Genetic results and DPWG guidelines can used by physicians and pharmacists to guide the dose and drug selection for the initial drug of inclusion, and for the prescription of any subsequent drugs that are newly started during follow-up and are on the list of drugs eligible for inclusion in PREPARE (i.e. a DPWG guideline is available for the drug). Physicians and pharmacists are given PGx test results but are not forced to adhere to the DPWG guidelines.

Study burden and risks

When a patient chooses to participate in this study, genetic information concerning 48 genetic variants in 13 pharmacogenes will be determined. Burdens to the patient are: 1) the supply of a blood or saliva sample for DNA collection, 2) being contacted four times at regular intervals by a research nurse (at baseline, four weeks and 12 weeks and at the end of the arm*s follow-up period), and 3) being asked to complete online surveys (at two weeks, and eight weeks). Patients who endure an ADR which is categorized as an *extreme phenotype* will be asked to provide an additional blood spot sample within 24 hours of the ADR. In a sub-study, patients included in the study for a first prescription of voriconazole, metoprolol, simvastatin, atorvastatin,

fluorouracil or capecitabine will be asked to provide additional blood spot samples at multiple time points and at the time of a serious ADR. Benefits to patients in the study arm include a potential reduced risk of ADRs. Overall, minimal risks are expected for included patients due to the fact that all of the drugs included within this study have previously been licensed for routine use and thus have been evaluated as having a positive benefit/risk ratio.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Subject must be >= 18 years old
2. Subject must receive a 1st prescription (meaning no known prescription for this drug in the preceding 12 months) for a drug of interest (Flecainide, Propafenon, Codeine, Tramadol, Capecitabine, Fluorouracil, Irinotecan,

Tamoxifen, Tegafur, Acenocoumarol, Clopidrogel , Phenprocoumon, Warfarin, Citalopram , Escitalopram, Paroxetine, Sertraline, Venlafaxine, Amitriptyline, Clomipramine, Doxepine, Imipramine, Nortryptiline, Phenytoin, Metoprolol, Efavirenz, Flucloxacillin, Voriconazole, Aripiprazole, Haloperidol, Pimozide, Zuclopenthixol, Atorvastatin, Simvastatin, Azathioprine, Mercaptopurine, Tacrolimus, Thioguanine or Atomoxetine), which is prescribed to them in routine care.
3. Subject is able and willing to take part and be followed-up for at least 12 weeks
4. Subject is able to donate blood or saliva
5. Subject has signed informed consent

Exclusion criteria

1. Previous (direct-to-consumer, or clinical) genetic testing for a gene important to the index drug
2. Pregnancy or lactating
3. Life expectancy estimated to be less than three months by treating clinical team
4. Duration of index drug total treatment length is planned to be less than seven consecutive days. A drug whose route of administration changes during the first seven days (e.g. intravenous to oral flucloxacillin) but whose total treatment duration is seven days or longer, is still eligible.
5. For inpatients: hospital admission is expected to be less than 72 hours (to facilitate acting upon the PGX results)
6. Unable to consent to the study
7. Unwilling to take part
8. Subject has no fixed address
9. Subject has no current general practitioner
10. Subject is, in the opinion of the Investigator, not suitable to participate in the study
11. Patient has existing impaired hepatic or renal function for which a lower dose or alternate drug selection are already part of current routine care. This would not apply to any drugs specifically given to manage liver/renal impairment/transplantation.
12. Estimated glomerular filtration rate (MDRD) of less than 15 ml/min per 1,73m2 in a subject with a functioning graft
13. Patients with advanced liver failure (stage Child-Pugh C)

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-03-2017
Enrollment:	1450
Type:	Actual

Ethics review

Approved WMO

Date:	15-03-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	24-05-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	10-07-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	25-08-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	01-12-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	29-05-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	28-08-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	01-11-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	31-01-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	11-06-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	30-06-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	11-03-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL60069.058.16