Pharmacogenetics Roll Out – Gauging Response to Service
[The PROGRESS Programme]

Protocol V6.0 25/07/2024
IRAS: 319800

Sponsors ref: B01739

CI: Prof William Newman

Amendment History

Amendment No.	Protocol Version and date	Details of Changes Made
NSA01	V1.1 17/05/2023	Dr Stuart Stewart and Alderley Edge GP Practice removed from list of Co-investigators. Addresses of co-investigators updated to Primary Care Networks from medical practices.
NSA02	V2.0 15/06/2023	Addresses of co-investigators updated to Medical Practices from Primary Care Networks
SA01	V3.0 28/06/2023	Section 3.3 updated to clarify who needs GCP training. Section 3.3.2.2.1 updated due to change in telephone consent process.
NSA03	N/A	Informed consent form updated to v2.1 17.08.2023, to amend a typographical error.
NSA04	V4.0 30/10/2023	Investigator list removed from the main protocol and added as an appendix (appendix B). Addition of 7 new participating sites to the co-investigators list in appendix B. Removal of reference to only 4 GP practices participating in the study. Correct error stating that participating sites are GP practices rather than PCNs. Updated signature statement.

		Clarification of who can refer a patient to the study, wording changed from 'physician' to 'health care professional'.
NSA05	N/A	Addition of a recruiting site for the PROGRESS study added to protocol appendix B
NSA06	N/A	Addition of a recruiting site for the PROGRESS study added to protocol appendix B
SA02	V5.0 09/02/2024	Introduction of e-consent as a method of remote consent, clarification of the details of results being returned in phase 2, change of study processes to allow samples to be returned via the post, changes to medicines listed in eligibility criteria, introduction of the use of buccal samples, removal of specific references to EMIS, changes to data storage and processing, extension to the study. PIS and ICF updated to reflect the above changes.
SA03	V6.0 25/07//2024	Changes made to clarify e-consent process and the e-consent platform that will be used. Introduction of posting kits direct to patients. Clarification of eligible combination Opioid Analgesics. Extension of study timelines.

This protocol has regard for the HRA guidance

This project will be conducted in accordance with the study protocol and the ethical principles outlined by Good Clinical Practice (GCP) and the Declaration of Helsinki in its most current version.

Signature Page

The sponsor signature on the IRAS form, acts as documented acceptance that the sponsor approves the protocol.

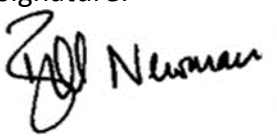
The Chief Investigator should sign below to confirm the following:

The Chief Investigator confirms the protocol has been agreed and accepted and agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:
Signature:



Date: 25/07/2024
Name: (please print): Professor William Newman

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i. Research Team & Key Contacts

Please see appendix B for a full list of the research team and key contacts

Chief Investigator:	**Professor William Newman** Address: Manchester Centre for Genomic Medicine, St Mary's Hospital, Manchester University NHS Foundation Trust, Oxford Road, Manchester, M13 9WL, UK Email: william.newman@mft.nhs.uk Telephone: 07525 009887
Sponsor(s):	Name: Manchester University NHS Foundation Trust, Manchester, M13 9WL Sponsor contact: Dr Lynne Webster Address: Research Office The Nowgen Centre 29 Grafton Street Manchester M13 9WU Email: lynne.webster@mft.nhs.uk Telephone: 0161 276 4125

ii. Glossary & Key Terms

Term	Abbreviation	Description
Clinical Pharmacogenetics Implementation Consortium	CPIC	An international organization which creates prescribing guidelines based on genotype.
Electronic Healthcare Record	EHR	An Electronic Health Record (EHR) is an electronic version of a patient's medical history. There are several EHR venders. EMIS is the EHR used by some of the practices in this study.
GEN-O	GEN-O	A platform which clinicians can access to review their patients' prescribing data.
Genomic Prescribing Advisory System	GPAS	The software developed by the authors of this protocol which converts raw genetic data

		into actionable prescribing information. The software is integrated into GEN-O.
Pharmacogenetics	PGx	Pharmacogenomics is the study of how genes affect a person's response to drugs – the focus of this protocol.
Primary Care Network	PCN	Groups of practices working together to focus local patient care.

iii. Study Summary

Title	Pharmacogenetics Roll Out- Gauging Response to Service (PROGRESS)
Lay Summary	The PROGRESS trial is part of a programme of work to introduce pharmacogenetic testing in primary care. A panel of genes with known implications for a range of commonly prescribed medicines has been selected and an informatic solution to help guide prescribing has been developed called the Genomic Prescribing Advisory System (GPAS). This pharmacogenetic testing and advisory system will be implemented at a number of GP practices to establish whether genetic testing can be delivered to support genotype-guided prescribing, in a clinically relevant timeframe and to assess any challenges to implementation.
Trial Participants	Patients attending participating GP surgeries who are being considered for a prescription in the following five medicine classes (Selective Serotonin Reuptake Inhibitors, Tricyclic Antidepressants, Statins, Proton Pump Inhibitors, Opioid Analgesics) or an agent change within one of these classes.
Planned Sample Size	1450 (Approx. 250 in phase I, 1200 in phase II) – Powered against primary outcome measure

Planned Duration	47 months total (13 months phase I, 16 months phase II, 6 months data collection, 12 months analysis)
Primary Objectives	To establish the proportion of patients who have a clinically relevant pharmacogenetic variant related to the medicine class which precipitated recruitment to the study.
Primary Outcome Measure (Whole Cohort)	The Pharmacogenetic Clinical Utility Metric (Defined as the proportion of patients across the study cohort with a CPIC Level 1A variant related to the medicine which triggered recruitment to the study)
Secondary Outcome Measures (Phase Specific)	Phase I – Service performance related outcomes e.g., can pharmacogenetic results be returned in a clinically relevant timescale. Phase II – Utilization of the pharmacogenetic data to guide prescribing e.g. Number of patients with at least one prescription amendment, proportion of study cohort with actionable pharmacogenetic variants, the proportion of enrolled participants for whom a clinical decision support notification was triggered, the average number of clinical decision support notifications which triggered over the course of the study.

iv. Funding and Support in Kind

Funder(s)	**Financial And Non-Financial Support Given**
NHS England Skipton House 80 London Road London SE1 6LH england.londonregionaldirector@nhs.net	**£531,000**

NIHR (Ref: NIHR301748) Central Commissioning Facility Grange House, 15 Church Street Twikenham TW1 3NL ccf@nihr.ac.uk	**£412,517**

v. Role of Study Sponsor and Funder

Manchester University NHS Foundation Trust is acting as sponsor for this study and is assuming overall responsibility for the initiation and management of the study. The Trust will provide permission to conduct the research and monitor the progress of that research. The research team all hold substantive or honorary contracts with the Trust and therefore the sponsor has influence over all aspects of the study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results which are the responsibility of the research team.

Funding is provided by NHS England to support the Genomic Medicine Service Alliance (GMSA) to deliver PROGRESS as part of a programme of transformational projects. The study is also supported by the National Institute of Health Research (Grant ref NIHR301748).

The overall project outline, including this study protocol, has been reviewed by NHS England as part of their funding approval process. Individuals from the national GMSA pharmacogenetics steering committee have also reviewed and commented on this protocol. The funders will not have any direct influence on data analysis and interpretation, manuscript writing, and dissemination of results.

vi. Roles and Responsibilities of Study Management Committees

Trial Management Group (TMG)

The Trial Management Group convenes weekly to ensure all practical details of the trial are progressing well and within the agreed milestones. The management group is chaired by the Chief Investigator and comprised of members of the Investigator team, including the key protocol contributors.

Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) has been established which shall meet formally on a 3 monthly basis, with monthly progress reporting from the TMG. This committee will be chaired by a General Practitioner external to the project and include representatives with expertise in informatics, pharmacy and health economics.

This steering group will monitor the performance and safety of the trial as well as advise on scientific and technical aspects of the project. The objectives of the TSC are to critically assess the ongoing results and identify any weaknesses, safety issues or delays. The membership are independent of the Sponsor and Investigators.

1. Introduction

Medicines are the most common therapeutic intervention in healthcare, yet the efficacy and safety of many drugs show considerable inter-personal variation.[1,2] Some patients are prescribed inefficacious medication, whereas others develop adverse drug reactions. This variation has a significant personal, clinical, and economic impact, leading to poorer individual and societal outcomes.[3,4] Strategies are required to reduce this variability. One approach is to leverage knowledge of an individual's genetic information to support medicines optimization, better informing medicine selection and dosing, a concept known as pharmacogenetics (PGx).

Almost half of all UK adults regularly take prescription medicines and the NHS's annual budget for medicines is approximately £22 billion per year, with over 1.1 billion items prescribed annually. Given this, even small improvements in effectiveness and safety could have significant health benefits at the individual and population level.

Evidence-based guidelines to support pharmacogenetic-guided prescribing are available for many commonly prescribed medicines, including clopidogrel, tricyclic antidepressants, proton-pump inhibitors (PPIs), statins and anticoagulants.[5–8] At the time of writing, the international multi-disciplinary group, the Clinical Pharmacogenetics Implementation Consortium (CPIC), have published 26 peer-reviewed guidelines outlining pharmacogenetic prescribing recommendations for medicines such as these.

Despite robust evidence, clinical implementation for PGx, especially in the UK, is limited to a few specific drug indications, namely azathioprine, abacavir, carbamazepine, and fluoropyrimidine chemotherapy agents. Current implementation typically involves a "reactive" testing strategy, where patients are tested for genetic variation relating to the medicine they are being prescribed at that moment in time. An alternative approach is "pre-emptive" pharmacogenetic testing, where a range of genes are genotyped in a non-specified time prior to the prescription of a given medicine. These data can then be integrated into a patient's medical records to inform the prescription of future medicines, throughout that patient's life. This approach has already been pioneered by several leading programmes in hospitals across the United States.

A 2020 analysis of the UK-Biobank identified 99.5% of participants carried an actionable pharmacogenetic variant, and 24% had previously been prescribed a drug for which they were predicted to have an atypical response.[9] Other studies, without the healthy volunteer bias which

can be seen in biobank research, have reported this figure being as high as 40%.[10] As such, there is a strong argument to be made for the use of wide-spread pre-emptive pharmacogenetic testing in the NHS.

In summary, sub-optimal medicines optimization is a globally important problem which costs lives and large sums of money. There is evidence that genotype-guided prescribing could contribute towards improved outcomes. At present, there is no definitive strategy in England for how pre-emptive pharmacogenetics should be implemented in practice, representing a major unmet clinical need. The North West Genomic Medicine Service Alliance, supported by NHS England, is developing this strategy.

As part of this multi-year project (named Pharmacogenetics Roll Out – Gauging Response to Service [The Progress Programme]) a pharmacogenetic gene panel has been selected for implementation and an informatic solution developed to support genotype guided prescribing. This informatic solution is known as the Genomic Prescribing Advisory System (GPAS). GPAS, which exists on an existing clinical interface known as GEN-O, has been designed to hold patient genotype and provide genotype guided prescribing advice for a range of medicines, based on peer reviewed CPIC recommendations.

As most prescription in the UK is initiated in primary care, we propose to test the roll out of pharmacogenetics in this setting initially. 90% of all patient-doctor interactions occur within General Practice, and therefore this represents an ideal and important arena to investigate pharmacogenetic testing. This protocol outlines the PROGRESS study, a pragmatic observational implementation study, which aims to assess the viability and utility of pharmacogenetic guided prescribing, via the GPAS system, in General Practice. Applying implementation science methodology, this initiative will test informatic solutions to deliver results to GPs and pharmacists, monitoring whether clinicians can utilize these data to practice genotype guided prescribing.

2. Study Objectives

2.1 Primary Question/Objective:

What proportion of patients have a clinically relevant pharmacogenetic variant related to the medicine class which precipitated recruitment to the study?

2.2 Secondary Question/Objective:

- Secondary Objective 1: Can pharmacogenetic data be delivered to primary care practitioners in a clinically relevant timeframe? And reasons for delays.
- Secondary Objective 2: Can pharmacogenetic data be used by primary care clinicians to inform genotype guided prescribing?
- Secondary Objective 3: What proportion of patients who have an actionable pharmacogenetic variant have their prescription amended as a result?
- Secondary Objective 4: What challenges emerge in implementation e.g., delays, prescription before results, non-use of pharmacogenetic guidance?
- Secondary Objective 5: Average time to prescription

3. Study Design & Protocol

PROGRESS is a pragmatic implementation study of genotype guided prescribing. The study will be split into 2 phases (Table 1).

Phase 1 Overview

- **Timeframe**: 13 months (months 1-13)
- **Recruiting Sites**: The pharmacogenetic service will be embedded into practice at early-adopter GP practices in the Northwest of England. All sites use the EMIS Electronic Health Record (EHR) system.
- **Sample Size**: A minimum of 250 Participants
- **Return of Results:** Results will be delivered via an external clinical portal (GEN-O).
- **Outcomes:** The primary outcome is the Pharmacogenetic Clinical Utility Metric (Defined as the proportion of patients across the study cohort with a CPIC Level 1A variant related to the medicine which triggered recruitment to the study). This is measured across the whole study (i.e., Phase 1 + Phase 2). The Phase I secondary outcomes focus on service-related

outcomes, assessing the performance of the testing pathway (i.e., can pharmacogenetic testing practically be delivered and used in a timely way in primary care).

Phase 2 Overview

- **Timeframe:** Approximately 16 months (months 14-29)
- **Recruiting Sites**: The study will expand to include at least one GP practice in each Genomic Medicine Service Alliance (GMSA) region in England. These will be identified during phase 1. All additional sites will use an EHR platform (e.g. EMIS or SystmOne).
- **Sample Size**: A minimum of 1200 Participants
- **Return of Results:** During this phase, results will be interoperable with the General Practice Electronic Health Record (EHR) with results surfaced as context specific "pop-ups" utilizing the practices existing clinical decision support provider. The GEN-O interface will still be available.
- **Outcomes:** The primary outcome will be measured across the whole study (i.e Phase 1 + Phase 2). The phase II secondary outcomes will assess patient focused outcomes, measuring the utilization of the pharmacogenetic data to support prescribing.

	Phase 1 (Months 1-13)	**Phase 2 (Months 14-29**
Recruiting Sites	Several early adopter GP practices in the Northwest of England	Phase 1 recruiting sites plus at least one GP practice in each GMSA region
Sample Size	250	1200
Return of Results	Via GEN-O	Direct into EHR via clinical decision support & Via GEN-O
Primary Outcome	Clinical Utility Metric*	
Secondary Outcomes	Performance of the Pathway	Utilization of the PGx data to guide prescribing

Table 1. Summary of the PROGRESS Study – Phase 1 and Phase 2. *The Clinical Utility Metric is defined as the proportion of patients across the study cohort with a CPIC Level 1A variant related to the medicine which triggered recruitment to the study

3.1 Participants

3.1.1 Sample Size

In total, a minimum of 1450 patients will be recruited to the PROGRESS study over a 29-month period. Sample size has been determined following statistical analysis (Section 8.1) and is powered against the study primary outcome. Recruitment will be split across 2 stages.

Phase 1: A minimum of 250 participants will be recruited over the course of 13 months

Phase 2: A minimum of 1200 patients will be recruited over the course of 16 months

3.2 Eligibility Criteria

All individuals will be considered for inclusion in this study regardless of age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion and belief, sex, and sexual orientation except where the study inclusion and exclusion criteria EXPLICITLY state otherwise.

3.2.1 Inclusion Criteria:

- Participants must be a registered patient at one of the recruiting sites.
- Participants must have capacity to independently consent.
- Participants must be 18 years of age or over.
- Participants being considered for a new prescription of one of five medicines classes, or participants being considered for an agent change within one of the five medicine classes (i.e., being switched from citalopram to paroxetine). The eligible medicine classes (and specific medicines) are:
  - **Selective Serotonin Reuptake Inhibitors** [citalopram, escitalopram, fluvoxamine, paroxetine, sertraline]
  - **Tricyclic Antidepressants (prescribed for pain or depression)** [amitriptyline, nortriptyline]
  - **Statin Therapy** [atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin]
  - **Proton Pump Inhibitors** [lansoprazole, omeprazole, pantoprazole]
  - **Opioid Analgesics [**Codeine, Tramadol] **Including Combination Products** (e.g. Co-Codamol).

Patients who have previously been prescribed one of the above medicines would be eligible for recruitment, providing they were not prescribed and adherent to the medicine at the time of

enrolment. If a patient were prescribed the medicine but had not been adherent (as determined by their clinician), they would be eligible for recruitment.

3.2.2 Exclusion Criteria:

- Patients unable to independently consent.
- Patients under the age of 18 years.

3.3 Recruitment Process

All research practitioners/research nurses completing the consent process and co-investigators will be fully GCP competent. The local co-investigator (PI at each GP Practice) will be responsible for clinical staff performing any duties in accordance with the protocol, ICH GCP and local requirements.

3.3.1 Identifying Participants and Providing Information

Eligible participants will be recruited from General Practice. During Phase 1, this will be from General Practices in the North West of England. Patients will be identified for recruitment by their primary care Health Care Professional (HCP)] or pharmacist as part of routine clinical practice [referred to herein as responsible Health Care Professional (HCP)]. Patients being considered for one of the five medicine groups, who also meet the other eligibility criteria (section 3.2), will be informed about the study.

Interested patients will be provided with a Patient Information Sheet (PIS) which describes the details of the study. This can either be provided as a physical PIS (if the patient is in a face-to-face clinic) or can be sent to the patient electronically from their practice. In the patient's electronic medical record, the recruiting clinician will be asked to use a predefined text template indicating the patient has been offered information on the study (including PIS version and date given), based on the anticipated prescription of a given medicine (coded as drug name and proposed dose). Patients will be informed that their contact details (e.g. telephone number) may be accessed by the research team, acknowledgement of this conversation will also be recorded. Patients will be asked to choose one of the three consenting models (section 3.3.2) – the preferred model will be online e-consent, but they will able to access any of the three models based on their preference and the availability of face-to-face appointments. If a face-to-face recruitment model is chosen, the patients will be given an appointment with a delegated member of the study team (including CRN team members where available) or staff from the GP Practice the same or following day at their practice.

If one of the two remote consenting models are chosen, the patients will provide verbal consent to be contacted by the research team to discuss the study and they will be given a recruitment pack containing a saliva kit or cheek swab, an instruction leaflet indicating how the participant can access the Castor e-consenting platform,and a stamped addressed box to return the sample via post.'The patient can either be given this recruitment pack at the end of their initial appointment (if initial appointment is face-to-face) or they can collect this from their GP practice (if initial appointment is remote) (Section 3.3.2). Verbal consent to contact, including permission to pass on contact details and details of triggering prescription, will be documented in the predefined text template in the EHR. The responsible HCP will then notify the research team that a patient has been identified via 1) sending a task to the research team within their electronic healthcare record (EHR), and 2) completing an online form (containing no patient identifiable information) which will alert the central research team via email that a patient is waiting at a given practice.

> *Case Example: [Day 0] Jack attends an appointment with their GP having had low mood for several months. It is decided to begin a course of antidepressants. The GPs preferred first line therapy is 20mg Citalopram once daily. This medicine is metabolized by the CYP2C19 enzyme. The patient is told that they may be eligible for enrollment in the PROGRESS study, which aims to assess whether genetics can be used to choose the best medicines for people. The patient would be told that this would mean receiving their prescription later than they would otherwise, approximately 7-10 days after enrollment. The patient indicates that they would be interested to participate. They are given a physical copy of the PIS, and they want to be recruited remotely via e-consent. As such, a recruitment pack, including a sampling kit is given to the patient. The clinician records the discussion in the patient's electronic notes, using the predefined template, and indicates that they would have received citalopram 20mg OD. They send a task to the research team within their electronic healthcare record (EHR) and complete the online form to alert the research team that a patient is awaiting recruitment.*

If the responsible HCP felt there was a clinical urgency to prescribe the medicine in the initial appointment rather than waiting until the pharmacogenetic data is returned, the patient could still be recruited. The clinician would prescribe the medicine and inform the patient that the study team would contact them as previously outlined. The pathway would otherwise remain the same except for how the return of the genetic results are handled (Section 3.4.3).

3.3.2 Recruiting Participants to The Study

3.3.2.1 Face-to-Face Recruitment

If the patient indicates that they would prefer to discuss the study in person, an appointment can be made with a delegated member of the study team, by the recruiting clinician. This appointment will either be at their own GP practice, at the Manchester Centre for Genomic Medicine (for Greater Manchester sites), or at a Clinical Research Network facility (where available). At these appointments, informed consent will be taken in person via a physical signature. The study will be explained in a manner appropriate to the potential participants' level of understanding and they will be given time to ask questions. At this appointment, an EDTA blood sample (3-5ml), a saliva sample, or a cheek swab (based on availability and patient preference) will be taken following consent. This will then be labeled with the patient details (Name, DOB, NHS Number) and will be sent to the North West Genomic Laboratory Hub for DNA extraction and testing. Samples will be sent, either by standard clinical pathways or pre-paid recorded-post, depending on the location of the recruitment site.

If the patient wishes to seek independent advice regarding whether to enroll in the trial, they will be afforded time to do this and will be contacted to continue or terminate the recruitment process the following day (via the remote process outlined below).

3.3.2.2 Remote Recruitment

There will be two distinct models of remote recruitment. The first, and preferred model, will be via online electronic consent – this will provide a scalable and equitable model for recruitment across England where multiple sites are involved in recruitment and access to clinic research network (CRN) support may be heterogenous across the country. Please note that electronic consent has been added as an amendment prior to phase 2, based on feedback from HCPs and patient representatives. The second model of remote recruitment is telephone consent and will be available to those individuals who wish to be recruited remotely but feel that they do not have the digital competency or access to technology to access recruitment online.

By using three distinct models (face-to-face, online consent, telephone consent) the study provides a recruitment approach which is flexible and scalable across multiple sites, whilst ensuring that potential participants are not excluded based on their access to technology.

3.3.2.2.1 Online E-Consent (Remote Model 1)

Patients who indicate that they wish to use an E-Consent model will receive a study pack from their GP Practice or direct to their home through the post. The pack contains a sampling kit (saliva or cheek swab) which is pre-labeled with a unique ID (I.e. GOLF-TANGO-TWELVE). The study pack has been designed with a purpose-built mailing system, so once the pack is opened, it can be resealed to post back to the study team (either via standard post-box or at any Post Office). The study pack will contain a URL and a QR code which, when followed, will take them to a dedicated recruitment platform for the PROGRESS study, built in collaboration with the e-consent provider - Castor. Once the participant has accessed the recruitment platform, they will be supported through the following steps:

1. The participant will arrive on the landing page which will be designed to provide a brief overview of the study and contain a patient-facing video explaining the study (PROGRESS Study video).

2. If the patient wishes to continue and they remain interested in participating, they will be asked to register their interest through this landing page by providing their email address.

3. The participant will then receive an email inviting them to create an account within the Castor eConsent platform (providing Name, DOB and gender).

4. Once an account is created, on logging in, they will be prompted to accept the invitation to the study and complete their study profile.

5. The participant will be able to remotely review, complete & sign the ICF within the Castor eConsent platform using an electronic signature – throughout this process they will have access to the PIS (via a hard copy provided with the pack) and an online version. The background video will also be provided throughout.

6. Once they have provided their signature remotely, they will be prompted to authenticate via their email address and password. All actions within the ICF (I.e. tick boxes and signatures) are tracked in the audit trail.

7. Once the patient has provided their consent, they will receive an email containing a web-based survey where they'll be asked to provide the unique sample ID (I.e. GOLF-TANGO-

TWELVE) found on the sample tube and provide the details of their GP Practice, ethnicity and known drug allergies.

8. The participant will then be able to complete the saliva sample and reseal it within the pre-addressed mailer solution provided with the study pack.

9. They will then need to post this in any Royal Mail post box or take it to a post office.

10. Once the patient has consented to the study, the central research team will receive an email notifying them of their enrollment. They will then review the ICF and countersign the document. The study team will then undertake a process of linking the patient's unique sample ID (i.e. GOLF-TANGO-TWELVE) with their study profile, which will be created on a REDCap database hosted on a Manchester University NHS Foundation Trust Server. The REDCap study profile, captures information from the patient's Electronic Healthcare Record (EHR) which the central study team will have access to.

11. Once the patient has been recruited, a record of enrollment will be made in their GP electronic health record (EHR) by a member of the research team. This will document the study details, the version of the PIS provided to the participant, the date on which the participant first received a copy of the PIS, and the date when informed consent was given. The record will also document that the patient has been provided with a copy of their ICF. This will be dated and signed by the individual who counter-signed the consent form.

This approach provides a methodology for recruitment which empowers the patient to register for the study at a time of their choosing and is not limited by the availability of physical recruitment space or clinical research network practitioner availability. However, although engagement work with HCPs and public participants suggests there is a demand for this approach, it is recognized that some participants may be excluded if this were the only modality. As such, face-to-face and telephone appointments are also available. When the patient begins an online E-Consent process (Model 1) but finds they have technical issues, a telephone number and email address will be provided for them to seek technical assistance. Where it is not possible to resolve the technical issues, the participants can default to a traditional telephone recruitment model (Section 3.3.2.2.2).

Where the potential participant has collected a study pack and indicated they wish to pursue an online e-consent model (model 1) but has not completed the e-consent process within 2 working

days of being identified by the HCP, they will be contacted by the research team to offer support if required. If they are unable to be contacted within the subsequent 3 working days, the responsible HCP will be alerted.

All material on the online platform will present information about the study in a manner appropriate to the potential participants' level of understanding and they will have time to consider their involvement. If they have any questions, they will be supplied with an email and a telephone number where they can discuss the study in more detail. If the patient wishes to seek independent advice regarding whether to enroll in the trial, they will be afforded time to do this as there is no time-limit for enrollment via the Castor e-consent platform.

3.3.2.2.2 Telephone Recruitment (Remote Model 2)

Patients who indicate that they wish to use a telephone remote consenting model will be contacted by a delegated member of the study team. The research team will be notified of eligible participants that have provided verbal consent to be contacted about the study via the online form and through a task on the electronic healthcare record.

During the initial telephone call the team will 1) answer any questions the patient has regarding the PIS, 2) complete a physical copy of the informed consent form (ICF) with the patient, 3) complete the recruitment proforma which will be made available via a REDCap database, and 4) support the patient in providing the saliva sample which was provided in the recruitment pack. The patient will be asked to read out their unique sample ID (i.e. GOLF-TANGO-TWELVE) and a record will be made by the central research team of the link between the sample and the participant. The study will be explained in a manner appropriate to the potential participants level of understanding and they will be given time to ask questions. If the patient wishes to seek independent advice regarding whether to enroll in the trial, they will be afforded time to do this and will be contacted to continue or terminate the recruitment process the following day. The sample will be labeled with the patient's identifiable information and should be posted in a Royal Mail letter box or at any Post Office the same or the next day. This will then be sent to the North West Genomic Laboratory Hub for DNA extraction and testing. The lead research team have processes to ensure consent is in place prior to any work on samples received for this study. In the unlikely event that a sample is received without consent having been correctly documented, the sample can be quarantined until consent is received or the sample will be disposed of.

3.3.2.2.3 Telephone Consent Process

Interested participants will be contacted by a delegated member of the study team as outlined above (Section 3.3.2.2) and will have access to the study PIS. If an individual wishes to enroll in the study, consent will be taken remotely via telephone. During this telephone call a member of staff will explain the study and take informed consent. The consent form will be signed by the delegated member of the study team and the patient will be posted a copy of their completed informed consent form for their records alongside a cover letter summarizing their involvement in the study.

All research practitioners will have access to each local instance of the patient's electronic healthcare record, meaning they can make an entry in their health record. Once the patient has been recruited, a record of the consent discussion will be made in this record. This will document the study details, the version of the PIS provided to the participant, the date on which the participant first received a copy of the PIS and the date when informed consent was given. Any questions raised by the patients will be noted and answers given will be documented. The record will also document that the patient has been provided with a copy of their ICF. This will be dated and signed by the individual who took consent.

3.3.2.3 Precedent for A Mixed Recruitment Approach

This Mixed approach mirrors the current practice in clinical genetics where consent for Whole Genome Sequencing (WGS), and recruitment to the National Genomic Research Library, can be taken remotely or in person. During recruitment, participants will be asked to consent for the following:

1. Blood, saliva, or buccal sampling for DNA extraction
2. Analysis of genetic material for genetic variation related to pharmacogenetics
3. That the genetic data can be interpreted and shared with health professionals involved in their care to support prescribing decisions.
4. That genetic information and prescribing advice can be shared with clinical decision support providers to move the data into their electronic healthcare record.
5. Permission to access their medical records for the duration of the study.

6. Permission to retain pseudonymized DNA samples for a maximum of 5 years after the end of the PROGRESS study to use as part of ethically approved research, carried out by the PROGRESS team.

7. Permission for clinical data to be transferred into their regional NHS Secure Data Environment (SDE) for processing and analysis.

8. The use of anonymized DNA samples to develop and validate new pharmacogenetic tests, which may involve sharing of anonymized DNA samples with researchers and organizations within and outside of the NHS.

Once the patient has consented to participate in the study, a recruitment proforma will be completed for each participant by the study team (in REDCap), which will assign the participant with a unique study ID. At recruitment, the study team will be asked to collect the following details.

1. Name
2. Date of Birth
3. Sex
4. Gender
5. NHS Number
6. Recruiting site
7. Allergy status/history of adverse drug reactions
8. Trigger for recruitment – This section will ask for A) The proposed drug (which triggered enrollment) and dose, and B) whether this is a new prescription within this class or a proposed switch within this class.
9. Ethnicity (self-reported)

3.3.2.4 Non-Attendance for Recruitment or Failure to Return Samples

The responsible HCP will be informed by the study teams that the patient has not been enrolled in the study, and therefore clinical action may be required, in the following situations:

- If the patient does not attend their scheduled face to face appointment with the research team member.
- If the study team are unable to contact the patient within 3 working days after the clinician noted the patient as interested in the study.
- If the patient does not sign up to the Castor e-consent system within 2 working days after the clinician noted the patient as interested in the study and the research team have then been unable to contact the patient in the subsequent 3 working days.

The responsible HCP will also be informed by the study team if the patient samples have not been received in the North West Genomic Laboratory Hub (NW GLH) five days after consent was given. In this situation, if the patient was recruited remotely the patient will be contacted to ensure the samples were returned to their GP practice or posted to the NW GLH, as advised. If the samples were returned appropriately, the responsible HCP will be informed that the results will be delayed, and a clinical action may be required (i.e., a decision to issue the prescription without waiting for the pharmacogenetic results).

Case Example: [Day 0] The GP practice added Jack to the contact list on the EHR after their initial consultation. [Day 1] Jack returns home and logs onto the Castor e-consenting platform, details of which are provided in the study pack he collected from his GP. He reviews the study documents online and decides he wishes to participate. The consent form is completed remotely via the Castor e-consent platform. He then receives an email advising him how to complete and register the saliva sampling kit enclosed in the study pack. He packages this in the mailer system provided and then posts this in a mail box, the same or next day. Jack did not need any support completing the consenting or sampling process but could have accessed this via the telephone number or email address provided, which would link him to the research team. Following consent, the research team receives a notification that a patient has consented to the study. They access the Castor e-consent portal, countersign the consent form, record consent on the patient's EHR, and create the REDCap Study Profile.

3.4 Study Procedures

3.4.1 Blood, Saliva or Cheek Swab Sampling

Participants who are recruited face-to-face will have a saliva sample, 3-5ml EDTA blood, or cheek swab taken before it is labelled with their clinical details. Samples taken from participants who

consent using one of the remote consent methods, will be labelled with either clinical details or a Unique ID (see remote consenting process). These samples will be sent, daily, via post (either clinical courier or royal mail depending on site) to the North West Genomic Laboratory Hub (GLH). There, DNA will be extracted and quantified in an NHS ISO15189 accredited laboratory before storage in the NHS DNA archive.

> *Case Example: [Day 2] Jack's saliva sample was posted the day after consent was taken. The sample was received by the North-West Genomic Laboratory hub the following day. [Day 3] DNA was extracted in the Manchester Centre for Genomic Medicine and transferred to the DNA archive.*

3.4.2 Genotyping

Genotyping will target a pre-defined set of frequent and clinically relevant variants across 20 pharmacogenes (around 75 gene changes in total). This is a test broad and report narrow approach. The results reported back to the responsible HCP will only be for the groups of medicines which are being assessed in this study (section 3.2.1). These are *CYP2C19*, *CYP2D6*, *CYP2C9* and *SLCO1B1*. With donor consent, samples will be kept in a pseudonymised form for 5 years after the study has finished to facilitate future ethically approved research.

Genotyping results will be exported to the electronic Genomic Prescribing Advisory System (GPAS) which has been built as part of the wider PROGRESS Programme. This In Vitro Diagnostic Medical Device (IVD) can convert the raw genetic data into actionable prescribing advice. The GPAS system exists on an IBM server as part of the GEN-O platform. This has been developed by academics and clinicians at the Manchester University NHS Foundation Trust. A Data Protection Impact assessment (DPIA) has previously been completed for the GEN-O platform ensuring that the system complies with data protection law. This DPIA will be updated considering the pharmacogenetic functionality and the commitment to share data across institutional boundaries.

> *Case Example: [Day 4] Jack's DNA sample is retrieved from the DNA archive and genotyped on one of the twice weekly pharmacogenetic genotyping runs. [Day 5] The results from the genotyping tests, once available, are exported to the GEN-O platform. This automatically converts the information into interpretable prescribing information. The results show that Jack is a poor metabolizer (PM) for CYP2C19, meaning he has greatly reduced CYP2C19 activity compared to normal metabolizers.*

The data will also be stored in a secure UK cloud-based clinical data repository developed for this study, known as PROGRESS-Rx. The storage system has been developed by the NHS North West Genomic Medicine Service Alliance (GMSA) in collaboration with Clinical Architecture. This storage approach allows the prescribing recommendations to be returned directly into Electronic Healthcare Records (EHRs) via Clinical Decision Support (CDS) providers (See section 3.4.4). A DPIA has been developed to support this programme of work.

3.4.3 Return of Results to the HCP (Phase 1)

During Phase 1, once the genetic data has been converted to prescribing advice by the GPAS software, the responsible HCP will receive a notification via email once the results for the patient they recruited are available. The results can be viewed via the GEN-O web-portal, which all recruiting clinicians and pharmacists will be able to access with a secure login. This will give specific prescribing advice for the drug-gene pair which stimulated recruitment and will also provide a searchable interface to allow the GP to query other gene-drug pairs in the future.

> *Case Example: [Day 5] Jack's GEN-O results undergo a final manual check by a member of the research team to ensure the data is displayed appropriately. The recruiting GP Practice and pharmacist are emailed informing them that the results are available to view. [Day 6] The GP or pharmacist review the results which show that Jack is a CYP2C19 poor metaboliser. This increases the plasma concentration of citalopram and can predispose to adverse effects. In discussion with the pharmacist, it is decided to prescribe Jack sertraline instead of citalopram, which is metabolized by both CYP2D6 and CYP2C19. This decision is recorded in the patient's electronic notes using a standardized proforma. The patient is contacted by the clinical team to discuss the treatment plan and issue the prescription. [Day 7] The patient collects their prescription.*

If the patient was already commenced on treatment due to a perceived clinical urgency (Section 3.3.1) then the patient will be contacted to consider whether their prescription should be amended. If the results show that the patient's pharmacogenetic profile is compatible with the initial choice of medicine, no further contact is specifically indicated outside of normal clinical practice. If the GP has previously agreed to contact the patient with the results of the genetic test, they can do so. However, this is not explicitly required within the protocol as some patients may just want to know the medicine is right for them, rather than a detailed discussion around the genetic results. The

patients can indicate that they wish to receive a copy of their results at the time of recruitment, which will be provided during phase 2 (Section 3.4.7).

3.4.4 Return of Results (Phase 2)

During Phase 2, prescribing guidance will be interoperable with the GP Electronic Health Records (EHRs) to allow for clinical decision support (CDS) triggers based on prescribing. The pharmacogenetic report, which relates to the initial recruitment trigger (i.e., should this patient be prescribed simvastatin based on their pharmacogenetic results?) will still be uploaded to GEN-O, and data will also be made available within the practice electronic health record via clinical decision support (CDS) functionality. This involves sharing clinical guidance within clinical decision support providers such as First Data Bank (OptmizeRx) and Optum (ScriptSwitch). These providers are already embedded within the GP practices involved in the PROGRESS study, where they provide the CDS functionality at these sites. The PROGRESS study has leveraged additional capabilities from these systems, specifically the ability to deliver in-context pharmacogenomic guidance. The responsible HCP will still be alerted (via email) once results are available. Making discrete pharmacogenetic data interoperable within the EHRs will allow CDS triggers for future prescribing decisions.

> *Case Example: During phase 2 (a year after Jack was enrolled in the study) he attends his GP with symptoms of gastroesophageal reflux disease (GORD). His GP proposes a trial of omeprazole 20mg once daily. The GP prescribes omeprazole via the electronic prescribing system. As Jack is a poor metabolizer for CYP2C19, a normal starting dose is appropriate, and no dose adjustments would be recommended. As such, the CDS does not trigger. If Jack were an ultrarapid metabolizer, with a heightened risk of therapeutic failure, a trigger would occur advising the clinician of the genetic result.*

A DPIA has been developed to support this programme of work and outline the data being securely transferred via the CDS providers.

3.4.5 Monitoring Pharmacogenetic Guided Prescribing

Once results have been returned, clinicians and pharmacists can make use of the genetic data and prescribing recommendations to support the prescribing decision which prompted recruitment. After reviewing the genetic data, the GP or pharmacist will be asked to use a template consult note (which will be searchable) in the EHR, to detail how they have used the data. The ambition is that pharmacogenetic results will be returned to the clinical teams within 10 working days of enrollment

(Figure 1). If there is a delay over this time, the clinical teams will be contacted, allowing them to make an independent clinical decision regarding whether to wait for the results or issue a prescription. This decision will differ depending on the specific clinical context.

3.4.6 Prescribing Guidance and Support

All prescribing recommendations used in the study will be based on the Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines for each medicine group (Appendix A). These are international consensus guidelines which outline how pharmacogenetic results should guide prescribing in specific clinical scenarios. The specific recommendations for each gene-drug pair will be approved by a panel of UK experts, which includes clinical geneticists, clinical pharmacologists, pharmacists, and general practitioners. The wording of the recommendations will be reviewed by a panel of clinical stakeholders including local GPs and pharmacists.

If prescribing recommendations are required beyond the level of detail provided in the GPAS system, the clinicians and pharmacists will be able to contact advice via the clinical genetics service at the Manchester Centre for Genomic Medicine. This will be via email (Response within 24 hours) or telephone (08.00-17.00).

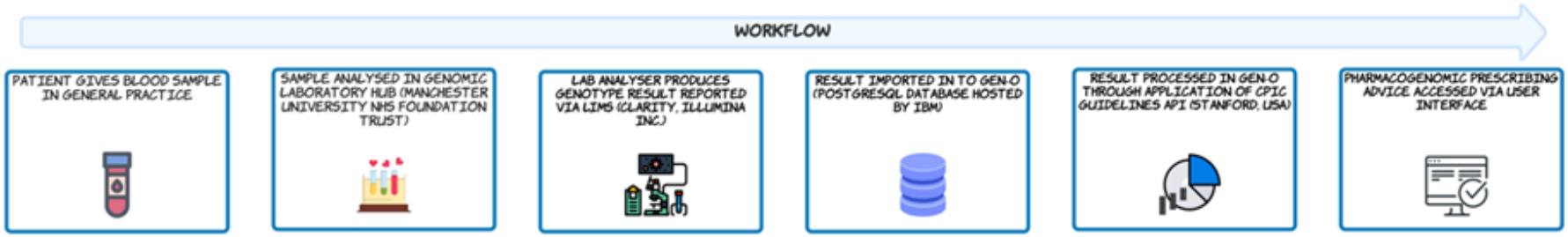

Figure 1. Phase 1 Testing and Results Workflow. The workflow for sample recruitment and return of pharmacogenetic data. Blood, buccal or saliva samples are taken in general practice or in another suitable location before being transferred to the Manchester Centre for Genomic Medicine's Genomic Laboratory Hub (GLH). The analyzer will produce the raw genetic data which is then imported to the GEN-O platform, hosted by IBM. The result is processed within the GEN-O platform using guidance from the Clinical Pharmacogenetic Implementation Consortium (CPIC). Results can then be accessed via the user interface (Phase 1) or directly via the EHR (Phase 2). The ambition is that, from the time of tissue sampling, genetic results will be returned to the clinical teams within 7-10 days.

3.4.7 Patient Access to Pharmacogenetic Data

During Phase 1, participants will not have direct access to their pharmacogenetic data or prescribing recommendations, however clinicians will be free to discuss any results with their patients. During Phase 2, all participants (including those recruited during phase I) will be able to request their results which will either be returned via a patient portal, built into the GEN-O platform, or via a PDF. They can do this by either indicating this on their initial consent form, or by contacting the study team, as described in the PIS. The way in which the results are returned will be optimized through existing PPIE programmes (see section 15) and through health informatic workshops via the University of Manchester.

3.5 Participants who withdraw consent

Participants can withdraw consent at any time without giving any reason, as participation in the research is voluntary, without their care or legal rights being affected. They can do this by contacting the study team. Contact details and the process for withdrawal will be provided on the PIS. Participants who withdraw their consent to be part of the study will have their data removed from the final analysis pipeline and their DNA sample will be destroyed. Their GEN-O profile will be deleted and, during phase 2, the pharmacogenetic data will be removed from their EHR. If a patient withdraws from the study whilst the results are still being generated, then the analysis of the DNA sample will be stopped, and results will not be returned. The recruiting HCP will be informed the same day and advised to revert to normal standard of care.

3.6 End of Study

The end of study is defined as 47 months after the study opens. This allows for 29 months of recruitment (13months Phase 1 + 16 months Phase 2), a further 6 months of data collection, followed by 12 final months of data analysis. Participants will consent for their prescribing data to be accessible for the duration of the study. They will also consent for their pseudonymised DNA samples to be made accessible for 5 years following this defined end of study point. These samples will only be accessed as part of ethically approved research programmes.

At the end of the study, it is anticipated that this pharmacogenetic testing approach will be approved as an NHS service and will be clinically validated. If this were to happen, the data will continue to be available for clinical use. If clinical approval has not taken place by the end of the study, then the pharmacogenetic functionality will be paused within the EHR, until approval has been granted. The pharmacogenetic metaboliser data will remain within the primary care record, even after the end

of the study, as this is part of the patient's clinical history and represents a discrete piece of health data. Though the pharmacogenetic data will remain part of the patient's health record, the corresponding clinical decision support functionality will not be operating to guide decision making. As such, any decisions made around prescribing based on the pharmacogenetic data will be individual clinical decisions, in line with current practice.

Once the study has completed, the relevant approval bodies (REC and MHRA) will be notified within 90 days. If the project is terminated early, this end of study notification will be submitted within 15 days with reasons given. The independent steering committee (Section 9) will review the average turnaround times of the testing on a monthly basis. If this committee feel that there are safety issues related to consistently prolonged turnaround times (>10 working day), or other safety issues, this committee reserve the right to suspend or terminate the study. It is the responsibility of the CI to notify the REC via the declaration of the end of study form available on the HRA website. A summary of the final research report will be submitted via email to the relevant REC within 12 months of the end of the study.

Study data and documentation will be archived in line with MFT policies and standard operating procedures. The study data will remain the property of MFT. A complete copy of the study data will be kept on the MFT secure IT server at the end of the study. At the end of the study all documents and data relating to this project will be stored securely at MFT for 10 years following completion of the project, or in line with MFT policies and in accordance with ICH GCP.

4. Outcome Measures

Outcome measures vary between Phase 1 and Phase 2. The outcome measures during Phase 1 will focus on process outcomes related to the efficiency of the testing pathway. Phase 2, over the course of the following 16 months, will longitudinally assess the utilisation of the pharmacogenetic data to inform prescribing decisions.

4.1 Study Primary Outcome:

The Clinical Utility Metric: The proportion of patients across the study cohort with a CPIC Level 1A variant related to the medicine which triggered recruitment to the study. [Mapped to primary objective]

4.2 Secondary Outcomes

4.2.1 Phase 1 Secondary Outcomes:

The proportion of patients recruited to the study who had their pharmacogenetic results returned within 10 working days (Monday – Friday) of enrollment. The day of enrollment represents day 0. [Mapped to Secondary Objective 1]

- Average turnaround time from enrollment to PGx results being available on GEN-O. [Mapped to Secondary Objective 1]
- The proportion of enrolled patients whose GPAS system record was accessed by a member of the clinical team. [Mapped to Secondary Objective 2 and 4]
- The proportion of participants who had a prescription issued before the pharmacogenetic results were available [Mapped to Secondary Objective 4]
- Average time from recruitment to prescription

4.2.2 Phase 2 Secondary Outcomes

- The proportion of patients who had at least one prescription amended over the course of the study based on the pharmacogenetic data. [Mapped to Secondary Objective 3]
- Average turnaround time from enrollment to results being integrated into the EHR [Mapped to Secondary Objectives 1 and 4].
- Proportion of participants who have a delay (more than 10 working days) in results being integrated into the EHR [Mapped to secondary Objective 4].
- The proportion of enrolled participants for whom a clinical decision support notification was triggered [Mapped to Secondary Objectives 2 and 3].
- The average number of clinical decision support notifications which triggered over the course of the study (expressed as per month/visit/prescription). [Mapped to Secondary Objective 3]
- The proportion of participants who had a prescription issued before the pharmacogenetic results were available [Mapped to Secondary Objective 4]
- The proportion of patients on a given class of medicine who had their index medicine (i.e., the medicine which precipitated recruitment) changed at 1and 6 months following prescription. This outcome will be compared against anonymized historical (non-genotyped) comparators,

matched for demographics, from the Greater Manchester Care Record (GMCR) or Secure Data Environments (SDE). [Mapped to Secondary Objective 2]

5. Data Collection, Source Data, and Confidentiality

As outlined above, once the individual has consented to participate in the study, an electronic recruitment proforma will be completed for each participant by the study team, which will assign the participant with a unique study ID. This will be stored in a REDCap database hosted on a Manchester University NHS Foundation Trust Server. REDCap is a secure web application for building and managing online surveys and databases. In this study, it is being used to host the online CRF and database.

The system is specifically designed for research and data is stored on an MFT server (not shared with any third party). MFT servers are backed up at the end of each day and are maintained by MFT Informatics Team. If data is lost, it can be recovered via the Trust IT back up service for the REDCap server.

Source data for this study consists of GP records stored in the EHR, other prescribing history from NHS records, EHR templates completed by the referring HCP, genotyping data (see section 6 and 7 below – this will be stored separately from clinical data) and prescribing guidelines. For patients recruited via online e-consent, demographic and contact data (supplied by the patient) will be stored by the Castor e-consent platform. Consent forms and consent information is stored within the e-consent solution. The Castor e-consent platform will be used which is a fully browser-based Software-as-a-Service solution, run on fully managed virtual secure private servers. The data will be held on a secure server in the EU or UK and all processing of personal data complies with General Data Protection Regulation (GDPR). No genetic or clinical data will be stored on the e-consent platform. A DPIA will be developed to support this programme of work and outline the data being securely transferred between the e-consent software and MFT servers.

Access to each GP practice's local instance of their EHR will be provided to the research teams who will be able to access these data for enrollment. Six-months after enrollment in the study, participants will have outcome metrics (Section 4) imported to the study database for analysis (Section 7). This will be undertaken by a research administrator who, as described above, will have access to each local EHR for research purposes. Individual access will be granted with appropriate letters of access, site level agreements or honorary contracts for research staff delegated to collect

data for the purpose of this study. These agreements ensure researchers are bound by the practice's confidentiality polices and gives permission for researchers to access data for these purposes.

Where possible, clinical outcome data will also be accessed via the NHS regional Secure Data Environments (SDEs). These resources make use of pseudonymised data for analysis, and consent will be sought from participants for data sharing, handling, and analysis within a secure environment.

All investigators and study site staff must comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing, and disclosure of personal information and will uphold the Act's core principles.

6. Sample Collection, Storage and Genotyping

As discussed above, 3-5ml of EDTA blood, a saliva sample (2mL), or cheek swab will be taken labelled with the participant's clinical details or recorded with a unique ID which can be linked to the patient. These samples will be sent daily via established NHS courier service or Royal Mail, to the North West GLH (NW-GLH), located in St Mary's Hospital, Manchester University NHS Foundation Trust. There, DNA will be extracted and quantified in an NHS ISO15189 accredited laboratory. Samples will be stored in the NHS NW-GLH in the DNA archive, a secure NHS facility which processes tens of thousands of DNA samples annually.

Genotyping will target a pre-defined set of frequent and clinically relevant variants across 20 pharmacogenes. With this type of genetic testing there is no possibility of incidental findings. With donor consent, samples will be kept for 5 years after completion of the study.

7. Study Databases and Analysis

Following source data collection there will be two REDCap databases. The first will contain the clinical data including 1) historical prescribing data (i.e. prescriptions issued prior to the commencement of the study), 2) contemporaneous prescribing data (i.e. prescriptions issued during the study), and 3) clinical outcome data (Section 4). The second database will contain the genetic information. Both databases will contain identifiable data and the study ID. For analysis purposes a final analysis dataset will be created 6 months prior to the end of the study, depositing the clinical and genetic data into a single pseudonymized dataset (labeled with study ID only) available for analysis by the research team (Figure 2).

Once the final study dataset has been created, the initial two datasets (which both contain the "key" to de-anonymize the final dataset) will be locked and the password protected by the senior investigator, Professor Bill Newman. These will be stored securely on MFT servers which ensures automated daily backup according to Trust IT policies. This procedure ensures that, at no stage during the final data analysis process, are the research team exposed to a dataset which contains both medication data and pharmacogenetic information, alongside identifiable information. As such, no potentially actionable prescribing recommendations will be apparent without them being passed back to the clinical teams as part of the study protocol. Please refer to the Data Management Plan (DMP) for more information.

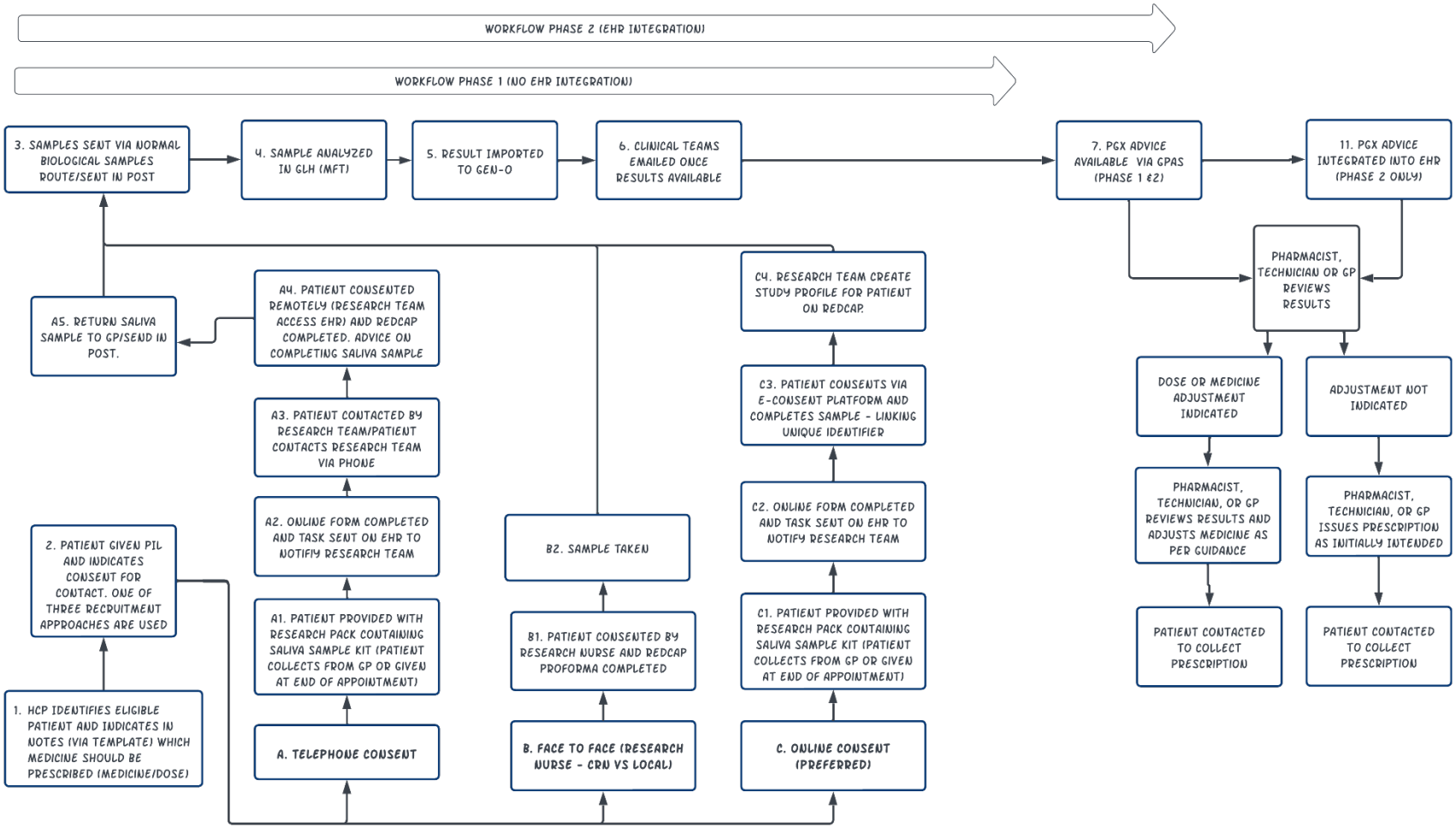

Figure 2. Recruitment and Data Analysis Workflow**.** Workflow for recruitment, return of pharmacogenetic data and handling of research data during the PROGRESS Study. PGx = Pharmacogenetics. GP = General Practice. ICF = Informed Consent Form. EHR = Electronic Healthcare Record, GPAS = Genomic Prescribing Advisory System, GLH = Genomic Laboratory Hub, MFT = Manchester University NHS Foundation Trust.

8. Statistical Considerations

8.1 Statistical Analysis

Phase 1

The proportion of reports delivered within 10 working days will be presented as a percentage and its 95% CI. This will be compared against the criteria for acceptability of the project to move on to the next phase. Reasons for failure to meet the 10 days target will be summarized. Average turnaround time will be presented by mean and SD or median and interquartile.

Phase 2

- The primary outcome will be expressed as a proportion and its 95% confidence interval of the whole cohort who had actionable variant related to the medicine class which precipitated recruitment to the study. Proportion of cohort who had actionable variant and were exposed to a medicine relevant to that genotype will be reported. These will be compared against those from existing control datasets available in the literature or locally (Specifically TARDIS, Vanderbilt, UK Biobank and IPTIP datasets).[24] The criterion for an actionable variant is as previously detailed (Section 2). Statistical differences in demographics, or recruiting site, will be tested between those with and without actionable genotype variant using appropriate tests.

- The proportion of patients on a given class of medicine who had their index medicine (i.e., the medicine which precipitated recruitment) changed at 1 and 6-months following prescription. This outcome will be compared against anonymized historical (non-genotyped) comparators, matched for demographics, from the Greater Manchester Care Record (GMCR).

- Reports delivered within 10 working days, prescriptions before PGx report, prescriptions amended as the result of PGx report and prescriptions not following the PGx report guidance will be presented by proportion and their 95% CI. Average turnaround time will be presented as a mean and 95% confidence interval or median and interquartile range depending on the distribution. Reasons for results not being ready within 10 days, reasons for prescription before PGx report and reasons for not following PGx report will be summarized and tabulated.

  Azita Rajai, medical statistician at the Manchester University NHS Foundation Trust, will provide statistical support for the project.

8.2 Sample Size

Sample Size: Determined based on the primary outcome for the whole study, i.e., - the proportion of patients have a clinically relevant pharmacogenetic variant related to the medicine class which precipitated recruitment to the study. Sample size is calculated using the formula $n = Z^2xPx(1-P)/e^2$ where z is value from standard normal distribution corresponding to desired confidence level (Z=2.326 for 98% CI), P is expected true proportion, e is desired precision.

Previous estimates from Vanderbilt, USA, suggest that 40% of individuals had a genetic variant related to a medication that they were prescribed. Given the diversity of the population in the United Kingdom, specifically in Greater Manchester, and the relative greater levels of medicalisation of healthcare in the USA, a lower prevalence of 0.3 will be chosen to represent P, with a desired precision of 0.03 and a CI of 98%. This results in a required sample size of **1263** across the study. We propose to recruit 1450 participants over the course of the study, 250 in phase 1 and 1200 in phase 2. This will allow for withdrawals and incomplete data (e.g. individual moves location).

The sample size for phase I has been chosen pragmatically (approximately 15% of the overall cohort), allowing the performance of the testing service to be assessed in a smaller group before increasing recruitment in Phase II. The decision to move from phase I to Phase II will be taken by the independent steering group who will need to be satisfied that turnaround times are adequate, there are not a high proportion of test failures, and there is capacity in the system to allow the increase in recruitment needed for Phase II. Transition to Phase II will only be possible if over 90% of participants have genetic results returned (a measure of the performance of the genetic test itself), and greater than 80% of patients have their results returned in 10 working days or less (a measure of turnaround time and existing capacity. A sample of 250 will allow observing 94% and 85% for overall return and return within 10 days with 95% confidence interval of (90%, 96%) and (80%,89%) respectively.

9. Data Monitoring and Quality Assurance

The study will be subject to the audit and monitoring regime of Manchester University NHS Foundation Trust in line with applicable MFT SOPs and policies. The study will have, as a minimum, an annual survey sent out for completion by a member of the research team.

An independent steering committee will be established who will be responsible for ensuring the fidelity of the study to the submitted protocol and will regularly review progress. Specifically, this committee will monitor the average turnaround times and synthesize feedback from each

of the recruiting centers collected at monthly meetings with each of the recruitment sites. Each site will also have access to an email address directly to the steering committee to raise concerns or provide feedback. This would not include identifiable or study information, but be limited to general feedback. Where the steering group deem that there are concerns regarding performance or safety, this will be reported to the PI with a recommendation whether to pause recruitment.

With participant consent, for 5 years after the end of the study, anonymized study data and anonymized samples can be shared with other academic and commercial research groups to aid the development of pharmacogenetic assays and to inform national and international strategies for implementation. All requests for data or sample export will be reviewed by the study steering committee and the PI. Any exported data will be fully anonymized to the external Centre.

10. Safety Considerations, Reporting and Adverse Events

The phased nature of the PROGRESS study, developed in co-ordination with clinical stakeholders, has been designed to maximize patient safety. Phase 1 will closely monitor process outcomes such as turnaround time and average time to prescription, ensuring that pharmacogenetic testing does not extend the time to commence treatment beyond 10 working days and the safety (AE related to delayed prescription, see below).

Once the pharmacogenetic testing results are available, the GP or practice staff will contact the participant to inform them that their prescription is ready. At this point, the participant will be asked to report any adverse events (deterioration in symptoms, development of new symptoms). These events will be recorded as part of the template consult note set up in the electronic healthcare record (EHR) for the GP/practice staff to complete when administering the new medicine. However, only those events which are thought to have been a direct result of waiting for their medication will be recorded as AEs/ SAEs by the research team, whether the delay is beyond the timelines outlined in the study (10 working days) or within the target timelines. If a participant contacts the site to self-report any change in symptoms, these can again be documented in the EHR and assessed by the clinician as whether directly linked to the delay in treatment, before being reported as an AE/SAE if applicable. It will be the responsibility of the reviewing clinician to define whether the patient has experienced harm and whether it is related to the study protocol. The research team will report any SAEs to the Sponsors. Any complications as a result of blood sampling for the study (bleeding, bruising) would be defined as an adverse event and would be reported via the EHR as above. All staff will be trained to take blood and recognize any complications. No other adverse events will be collected for this study.

Where there is uncertainty about the definition of an adverse event, the PI will review the event with the recruiting clinician to make a judgement.

As this is an implementation trial, any side effects or treatment failure arising from the chosen course of medication would not be considered an AE in this study, as all treatments are standard of care options.

The core study team based at MFT will meet monthly to discuss potential safety concerns. A steering committee will also be convened to meet every 3 months to provide oversight and advise on possible safety issues. This committee will be chaired by a General Practitioner external to the project and include representatives with expertise in informatics, pharmacy and health economics.

11. Peer Review

An outline of this protocol has been reviewed by NHS-England who, based on the proposal, approved funding for the PROGRESS Programme from 1 April 2022. The full protocol has been read and approved by the national GMSA steering committee. Subsequent amendments have been reviewed by the study steering committee and aspects of the protocol designed with HCP and public stakeholders.

12. Ethical and Regulatory Considerations

12.1 Approvals

Before the start of the study, a favourable opinion will be sought from an NHS Research Ethics Committee (REC) for the study and all the supporting documents including the protocol, information sheets, informed consent forms and other relevant documents. The study team will be responsible for the maintenance of a study site file, in which all current and superseded study documents will be retained. Also contained in the site file will be the approval documentation including correspondence with relevant authorities such as the HRA and REC. The study team are responsible for producing progress reports throughout the study, including annual reporting (APR) to REC as required. The Chief Investigator will notify the REC of the end of the study, and will submit a final report with the results, including any publications/abstracts, to the REC within 12 months of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. No participants will be enrolled into this research study prior to the study being reviewed by the relevant regulatory authorities and receiving HRA and REC approvals, as well as approval from the R&I office at Manchester University NHS Foundation Trust.

This study will be subject to ethical review by an NHS Research Ethics Committee (NHS-REC) and the Health Research Authority (HRA). The study will be conducted in full conformance with all relevant legal requirements and the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and the UK Policy Framework for Health and Social Care Research 2017.

Following discussion with the MHRA, the GPAS system will be considered an In Vitro Diagnostic (IVD) medical device as per the EU medical device directives 93-42-EEC. For the purposes of this clinical study, we will notify the MHRA of our intention to carry out a clinical investigation as outlined on the MHRA website (https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device). The study will be registered on the ISRCTN registry, and the protocol will be published in an open-access journal prior to completion of the study.

12.2 Amendments

Any amendments to the study shall be reviewed by the sponsorship team prior to submission. Any non-substantial amendments shall be notified to the HRA and any substantial amendments, along with amended documentation, shall be approved by the REC, and HRA, prior to implementation as per nationally agreed guidelines. The Chief Investigator or designee will work with the R&I department to put the necessary arrangements in place to implement the amendment and to confirm their support for the study as amended.

12.3 Risks

The phased nature of the study, developed in co-ordination with clinical stakeholders, has been designed to maximize patient safety and minimize risk. The main risks are in relation to the blood sampling, the delay to initiation of medicines, and the recommendation of alternative medicines based on pharmacogenetic guidelines. These are outlined and discussed below.

1. The participant has a small risk of bleeding or bruising after phlebotomy, but not above that of normal clinical practice.

2. All participant DNA samples will be stored securely within the NHS NW GLH laboratory based at St Mary's Hospital, MFT which has extensive experience handing such samples and is ISO15189 accredited. As such, the risk of DNA contamination or loss is very low. No genetic testing outside that described in this protocol will be conducted on the sample without explicit informed consent under relevant ethical approval.

3. Identifiable participant data will be stored in secure password protected databases and any clinical or genetic data will be hosted on servers within the NHS. Data

will also be stored the Castore-consent platform, which is a fully browser-based Software-as-a-Service solution, run on fully managed virtual secure private servers. The data will be held on a secure server in the EU or UK and all processing of personal data complies with General Data Protection Regulation (GDPR). No genetic or clinical data will be stored on the e-consent platform. As such, the risk of data loss or breach is very low. Any researchers delegated to work on this study will have appropriate agreements in place to allow access for data collection for this study. More information on data collection and confidentiality is described in Section 5. Confidentiality of data is a key consideration and therefore a decision has been made to pseudonymise the final dataset. Complete de-identification would preclude follow up analysis, and therefore this has not been included in the protocol.

4. There is a risk of a minor delay to medicine initiation whilst waiting for pharmacogenetic test results. For example, medicines would not be initiated in the initial clinic appointment but might be dispensed the following week (7-10 working days), once pharmacogenetic guided prescribing can take place per protocol. The medicine classes (PPI, antidepressants, and statins) have been specifically chosen (with support of clinical stakeholders) as they are rarely, if at all, prescribed urgently in primary care. As such, this minor delay is highly unlikely to be to the detriment of safety or clinical outcomes. If the clinician feels that there is a clinical urgency to prescribe the medicine at the first appointment, and consider an adjustment once pharmacogenetic results are available, then this is permissible within the study protocol (Section 3.3.2).

5. The prescribing recommendations in this study are based on guidance from the Clinical Pharmacogenetic Implementation Consortium (CPIC). There are dedicated guidelines, outlining recommended prescribing behavior based on genotype, for statins, SSRIs, TCAs, Opioids, and PPIs.[6–8,11] The recommendations either guide dose adjustment (on label) or recommend another medicine which the patient is more likely to respond to. These guidelines are peer-reviewed and internationally recognized. They are used as part of routine clinical practice in many centres across the world. There is a theoretical risk that a participant who may have responded to the initial medicine of choice (i.e citalopram) is switched to an alternative agent (i.e. sertraline) which they may not respond to.[8] Based on existing data, it is expected that this risk is low and that pharmacogenetic guided prescribing will, overall, improve the safety and effectiveness of medicines. The guidelines change infrequently and with minor amendments. As such,

there is a very low likelihood there would be a significant update to these guidelines during the study. However, both Professor Newman and Dr McDermott are members of CPIC, therefore the research team would be made aware of any updates with at least 12 months' notice. In the unlikely scenario where a clinically relevant update takes place, there would be ample time to change the guidance within the clinical decision support software and apply for any ethics amendments where required.

13. Finance and Insurance

The study is supported by an NIHR Fellowship Award (NIHR301748) and by NHS-England through the North West Genomic Medicine Service Alliance (GMSA). Study recruitment support has been approved by the Clinical Research Network.

The NHS indemnity scheme will apply to this study to ensure it meets the potential legal liability of the sponsor, equipment, employer, and investigators/collaborators for harm to participants arising from the management, design and conduct of the research. No arrangements will be made for the payment of compensation in the unlikely event of harm.

14. Dissemination and Publications

Findings, positive or negative, will be published in leading peer reviewed journals and presented at international conferences. The protocol will be published and registered via the ISRCTN Registry. A dedicated PPIE dissemination strategy will be developed with our existing PPIE group which has been established for this study. Participants will be able to request on the ICF that they wish to know the outcome of the study. If they do, they will be sent an electronic copy of the published manuscript with a patient summary sheet.

15. Patient and Public Involvement and Engagement (PPIE)

In preparation for the PROGRESS study, a patient and public engagement group was established to provide feedback on various aspects of the study. This group meets every 4 months and has representation from a diverse group of individuals with experience of taking medicines. Key aspects of the protocol were discussed with this group during drafting of the protocol, with a specific focus on a) the recruitment process and b) the process for returning results. This co-design process led to an improved protocol, reflecting the views and concerns of the patient representatives. We will continue to work with this group to optimize the way in which pharmacogenetic results are returned to participants, which will be introduced during phase II.

The group will continue to sit 4 monthly during the lifetime of the PROGRESS study and will be available to review any amendments or methodological queries which might arise. This group will also be involved in the eventual process of interpreting and disseminating the findings.

16. References

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Appendix A – CPIC Prescribing Recommendations
Statin Therapy and SLCO1B1

https://cpicpgx.org/guidelines/cpic-guideline-for-statins/

SSRI Therapy, CYP2D6 and CYP2C19

https://cpicpgx.org/guidelines/guideline-for-selective-serotonin-reuptake-inhibitors-and-cyp2d6-and-cyp2c19/

TCA Therapy and CYP2C19

https://cpicpgx.org/guidelines/guideline-for-tricyclic-antidepressants-and-cyp2d6-and-cyp2c19/

PPI Therapy and CYP2C19

https://cpicpgx.org/guidelines/cpic-guideline-for-proton-pump-inhibitors-and-cyp2c19/

Opioid Therapy and CYP2D6

https://files.cpicpgx.org/data/guideline/publication/opioids/2020/33387367.pdf