RESEARCH PROTOCOL

The *Implementing Pharmacogenetics to Improve Prescribing (IPTIP) Trial*

Contents

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2. INTRODUCTION

Medicines are the most common therapeutic intervention in healthcare, yet the efficacy and safety of many drugs show considerable inter-personal variation. 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. Strategies are required to reduce this variability. One approach is to leverage knowledge of an individual's genetic information to support medicines optimisation, better informing medicine selection and dosing (pharmacogenomics).

Evidence-based guidelines to support pharmacogenetic-guided prescribing are available for many commonly prescribed medicines. Despite a good understanding of these medicine-gene relationships, clinical implementation in the UK is limited to a small number of medicines. This is typically carried out reactively, where single genes are analysed when a medication is considered.

Given the high population frequency of genetic variation which influences the efficacy and safety of medicines, an alternative approach to pharmacogenetic guided prescribing is pre-emptive panel testing. This involves testing individuals for many common pharmacogenetic variants at a set time, irrespective of the medicine they are prescribed. This information can then be integrated into a patient's medical records and used to inform prescription. Currently, there is limited evidence suggesting how such an approach would impact on prescribing behaviour in the UK.

The Implementing Pharmacogenomics to Improve Prescribing (IPTIP) trial is a cross-sectional study linking patient genotype with prescribing data to measure the clinical utility of pre-emptive pharmacogenetic panel testing. This will determine the potential clinical value of the approach, both in the primary and secondary care settings, and identify key cohorts where targeted testing might be most appropriate. Implemented effectively, pharmacogenetics has the potential to improve patient outcomes. The output from the IPTIP trial will inform the development of a local and national pharmacogenetic service.

3. BACKGROUND

3.1. What is the problem being addressed?

It is a well-recognised clinical phenomenon that patients display variation in their response to medicines.[1] Consider three patients in pain, all prescribed the same dose of codeine. The first responds appropriately, the second appears to receive no analgesic relief, whilst the third develops symptoms of opioid toxicity. Such variation in response and side-effects is a frequent and often frustrating feature of clinical practice.

Such variation is regularly attributed to the chosen dosing strategy, the accuracy of the initial diagnosis or individual factors, such as co-morbidities, polypharmacy or compliance.[1] There is evidence that response to a medicine is impacted by an individual's genetic make-up, a concept known as pharmacogenomics. Codeine requires activation to morphine by the hepatic cytochrome CYP2D6.[2] Common genetic variants in the *CYP2D6* gene impact the function of the CYP2D6 enzyme. Considering the above scenario, the second patient, like 10% of the population, may be a poor CYP2D6 metaboliser, meaning they fail to effectively convert codeine into morphine. Meanwhile, the third patient may represent approximately 2% of individuals who are ultra-rapid CYP2D6 metabolisers, in danger of producing high morphine levels, leading to toxicity.

Codeine is just one example of a medicine with evidence for informing prescribing based on genotype. Good evidence exists for many other commonly prescribed medicines including clopidogrel, tricyclic antidepressants, proton-pump inhibitors (PPIs), statins and anticoagulants.[3–7] Despite this, clinical implementation, especially in the UK, is limited to a few specific indications, namely azathioprine, abacavir and fluoropyrimidine chemotherapy agents.[8–10] 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. Many argue

that a prospective testing approach, using gene-panels, is a preferable model.[11–13] Proponents cite the high prevalence of clinically relevant pharmacogenetic variants in the population and the widespread use of medicines for which pharmacogenetic dosing-guidelines exist.

There is evidence to support genotype-guided prescribing for a range of medicines and the cost of genetic sequencing has fallen to allow use in clinical practice.[12,14] Despite this, there are remaining barriers to prospective pharmacogenetic testing, as evidenced by the lack of clinical implementation across the UK. These barriers were recently discussed as part of a policy discussion, and the contributors specifically highlighted a paucity of evidence around real-world clinical utility.[11,15] **The IPTIP trial aims to address this, by determining the clinical utility of pharmacogenetic data using both historical and contemporaneous prescribing data.**

In this proposal, clinical utility refers to the concept that an individual would have their prescription altered based on their genotype. A cross-sectional survey of US veterans found 99% carried an actionable pharmacogenetic variant.[16] However, many of these variants were related to the metabolism of medications that the patient is not prescribed; therefore, clinical utility in those patients is low. Defining the clinical utility of pharmacogenetics on a more granular level is critical when considering implementation strategies. If overall clinical utility is high, then a pre-emptive panel approach is likely to be a practical approach, otherwise, more targeted testing strategies may be appropriate. The integration of pharmacogenetics within clinical practice represents a complex intervention, as defined by the Medical Research Council, and causal assumptions which underpin any intervention should be well characterised before implementation.[17] **By linking genotype and detailed prescribing data, the IPTIP trial will define clinical utility and identify cohorts where pharmacogenetic testing is of particular benefit.**

3.2. Why is this Research Important?

Medicines are the most common intervention in healthcare. Almost half of all UK adults regularly take prescription medicines.[18,19] The NHS's annual budget for medicines is approximately £17.4 billion per year, with over 1.1 billion items prescribed.[11,20] Given this, even small improvements in effectiveness and safety could have significant health benefits at the individual and population level. As such, The Royal Pharmaceutical Society promotes medicines optimisation, which aims to ensure that the patients get the right medicine, at the right dose, at the right time.[18]

Effective medicines optimisation is important on both an individual and a societal level. Adverse drug reactions (ADRs) account for 6.5% of hospital admissions and 14.7% of extended hospital stays.[21,22] This equates to approximately 8000 hospital beds occupied at any one time, estimated to cost the NHS £1.6 billion per year. There is good evidence, for multiple gene-medicine pairs, that pharmacogenetics could be used to improve efficacy and to reduce the rate of ADRs.[12] **The IPTIP trial aims to investigate the clinical utility of pharmacogenetics which will contribute to improved strategies for medicines optimisation, increasing efficacy whilst reducing ADRs.**

A 2018 analysis of a primary and secondary care prescribing found that PPIs, statins, antiplatelets and antidepressants were some of the most commonly prescribed items.[23] All of these classes of medicine have guidelines for genotype-guided prescribing. Polypharmacy (concurrent prescribing of medication) is common. There is evidence to suggest that if patients are prescribed a medicine with pharmacogenetic guidance, they are highly likely to also be prescribed other medicines with similar guidelines.[24] As such, panel testing could be a powerful approach to optimise an individual's whole prescription, rather than a single medicine. In addition, once generated, these data will remain valuable throughout an individual's life.

Integrating pharmacogenetics into clinical practice has the potential to lead to improved effectiveness and reduce ADRs, therefore optimising patient outcomes whilst using NHS resources effectively. To achieve effective integration, it is necessary to measure the clinical utility of pharmacogenetics, and design intelligent implementation strategies reflective stakeholder preferences.

There is a significant unmet need to better understand the clinical utility of pharmacogenomics. Recognising this, the IPTIP trial has been fully funded by the National Institute for Health Research (NIHR) based on the protocol below, which was reviewed as part of the application process. The award for the study forms part of a Doctoral Research Fellowship (DRF) award for Dr John McDermott. In summary, the results from this work will have broad applicability and will contribute to the design of services, on both local and national levels, which will improve outcomes for patients across multiple clinical specialities.

4. STUDY OBJECTIVES

4.1. Primary Question/Objective:

If a pre-emptive pharmacogenetic test were implemented, what proportion of patients would have their prescriptions adjusted based on the results?

4.2. Secondary Question/Objective:

Are there specific groups of patients in whom pre-emptive screening would be of heightened value?

5. STUDY DESIGN & PROTOCOL

5.1. Participants

A minimum of 646 participants will be recruited across two groups. Participants will be recruited from an outpatient (IPTIP-O) and inpatient (IPTIP-I) setting at the Manchester University NHS Foundation Trust (MFT). As the largest acute hospital trust in the UK, recruitment will access a population from diverse ethnic and socio-economic backgrounds.

- **IPTIP-I**: Patients admitted to the Manchester Royal Infirmary (MRI) will be recruited. The MRI is large tertiary referral centre with over 750 medical and surgical beds and the Acute Medical Unit (AMU) has a throughput of approximately 200 patients per week.
- **IPTIP-O**: Patients and their relatives who have an outpatient appointment with the Manchester Centre for Genomic Medicine (MCGM) or have previously had an outpatients appointment and are still in follow up with the clinical genetics service, will be eligible for recruitment. The MCGM serves a population of 5.7 million and there are over 10,000 appointments each year.

5.2. Study Intervention and/or Procedures

For the Inpatient arm (IPTIP-I), eligible patients admitted to the Manchester Royal Infirmary will be provided with a written Patient Information Leaflet (PIL) after admission to the ward. Participants will be provided as much time as they wish to consider participation before written informed consent is taken. Those meeting eligibility criteria will be approached by the study team, and consent will be taken whilst on the ward. Consent will be taken by a delegated member of the research team or clinical team involved in the patient's care.

Adults who have an appointment with the MCGM will be identified by the reviewing clinician. For the outpatient arm (IPTIP-O), participants will be given a patient information leaflet (PIL) and a clinic room will be reserved for recruitment where the patient is seen face-to-face. Where the patient has been reviewed virtually, the PIL can be sent via post or e-mail. For IPTIP-O recruitment, consent will be taken at the time of the appointment where the patient is attending face to face, or via the completion and return of a consent form via the post where the patient has had a virtual appointment. The consent form will be posted with a freepost envelope included to return.

For the IPTIP-I arm, all consent will be taken or over during the participant's admission (IPTIP-I).

5.3. End of Study

The end of study will be defined as the date of the last participant recruited plus 6 months for data analysis. Participants will consent for their prescribing data to be made accessible for 5 years following this defined end of study, to allow time to monitor future prescribing practice.

6. STUDY PARTICIPANTS

6.1. Inclusion Criteria:

- Participants must be admitted to the Manchester University NHS Foundation Trust *or have* attended an outpatient appointment, as a patient or relative/carer/partner, at the Manchester University NHS Foundation Trust
- Participants must have capacity to independently consent
- Patients must be over the age of 18 years.

6.2. Exclusion Criteria:

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

6.3. Recruitment:

As outlined above (section 5.2), recruitment will take place in 2 locations at a single site. The recruitment approach will differ slightly between IPTIP-I and IPTIP-O. All patients will be asked to consent to the following:

1. Blood sampling for DNA extraction **or** saliva sampling for DNA extraction (if difficulties in obtaining a blood sample as first choice) **or** access to stored DNA where a sample has already been taken for a previous clinical indication.
2. Access to inpatient prescribing data
3. DNA analysis related to pharmacogenetics
4. Sharing of identifiable data with Graphnet CareCentric, who operate the Greater Manchester Care Record (GMCR), to allow data retrieval from primary care records.
5. Access to historical and future healthcare data via the Greater Manchester Care Record (GMCR)
6. Transfer from the Greater Manchester Care Record (GMCR) into the NHS GM Analytics and Data Science Platform (ADSP) for analysis and storage for a maximum of 5 years after the end of the IPTIP study.
7. Where access to the GMCR is not possible, because the patient is not registered with a General Practitioner in Greater Manchester, permission will be sought to access prescribing history via the Summary Care Record (SCR).
8. Sharing of anonymized data and patient samples for ethically approved research.
9. Patients will have the **option** of consenting for a buccal sample (cheek swab) to be taken alongside the blood or saliva sample. This will be used to assess whether it is possible to test for the pharmacogenetic variants more quickly using a non-invasive sample.

6.3.1. IPTIP-I Recruitment

The acute medical unit (AMU) at the Manchester University NHS Foundation Trust (MFT) is 48 bedded unit. This represents one of several acute wards at the Manchester Royal Infirmary. Recruitment will take place in one of three wards (AMU, Manchester Vascular Centre, and the Acute Care Unit) – ensuring a diverse cohort of patients are recruited. Each day during the recruitment period a randomised list of the beds across the three wards will be generated, and the patients will be approached in this order, minimising sampling bias to avoid the sample being skewed towards those more amenable to recruitment such as the young or English speaking. This approach will endeavor to ensure that individuals across all age groups, both sexes and all ethnicities are included. Every month, average participant demographics will be compared against existing control data to ensure a representative sample of the inpatient population is being recruited. The patients will be approached by the direct clinical or research team (CRN research support and sub-investigators), the study will be discussed and a PIL will be provided. Thereafter, if the patients wish to enrol, a

consent form will be signed, blood or saliva (+/- buccal) samples for DNA extraction will be taken and the initial recruitment proforma will be completed, generating a unique study ID.

6.3.2. IPTIP-O Recruitment

The MCGM serves a population of 5.7 million and there are over 10,000 appointments each year. Participants will be recruited from the MCGM outpatient department, a dedicated unit where a clinic room will be reserved for IPTIP recruitment. Anyone attending the MCGM, including the consultee and their relatives, carers or partner, will be eligible for recruitment, within the scope of the exclusion criteria as described above (Sections 6.1 and 6.2). Participants will be identified by the reviewing clinician in clinic, or by writing to patients who have previously been seen in the department and are still under follow up with the clinical genetics service. As a result of the COVID-19 pandemic, there is an approximately 50:50 split between face-to-face and virtual clinic appointments. As such, we propose both face-to-face and virtual consenting processes, to facilitate recruitment and ensure those who cannot travel as easily are not prevented from participating. For face-to-face appointments, interested individuals will be invited for a discussion with the research team in the reserved consultation room and the study will be discussed, during which a PIL will be provided. If patient's wish to have more time to consider the study, they will be offered a follow up telephone or videocall. Where patients wish to enroll during clinic, a consent form will be signed, blood/saliva samples for DNA extraction will be taken (if a stored sample not already available) and the initial recruitment proforma will be completed, generating a unique study ID.

For virtual appointments or where patients indicated they would like more time to consider the trial, a telephone or video call (NHS Attend Anywhere or Microsoft Teams) will be arranged with the research team to discuss the study. Following this phone call if the patient is happy to receive information about the study, an information sheet and consent form will be posted to the participant with a pre-addressed return envelope. A short data collection form will be included with the consent form for patients to complete. This will allow accurate collection of demographic and drug allergy information, which would usually be completed as part of the initial recruitment proforma, if the patient was seen in a face to face clinic. If the patient wishes to participate, then they can return the completed consent form and data collection sheet in the pre-addressed return envelope. The contact details for the research team are on the patient information sheet should the patient wish to discuss the study with a member of the team after reading the patient information

sheet. If a DNA sample is already available then this will be accessed for the study, otherwise an appointment will be made for the patient to have their bloods taken for DNA extraction or a saliva sample will be sent in the post for completion and return. Where patients are contacted by letter to inform them about the trial, they will be offered a virtual consultation or a face to face appointment at their convenience.

If a patient has been sent the study information and has not returned a completed consent form after one month, then the research team may make contact with the patient to see if they are still interested in participating in the study and re-send the study information if required.

Each month, average participant demographics will be compared against existing control data to ensure a representative sample of the population attending the MCGM is being recruited. This data will then be fed back to the recruiting clinicians facilitating more tailored recruitment. Information regarding the trial will be placed on the North West Genomic Medicine Service Alliance (GMSA) website. This will be patient facing material (Appendix 2) which will provide information on the study and advise how interested participants can become involved.

6.4. 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. 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. This will be made possible by de-anonymizing the final dataset via the secure study key (Section 8.3).

7. OUTCOME MEASURES

The Primary outcome is the proportion of patients with a genotype related to a medicine they are currently, or have previously been, prescribed. Genotype-phenotype relationships will be assigned where there is high level PharmGKB evidence for clinical actionability (Levels 1A or 1B). Rates for the whole cohort will be presented but will be split by recruiting site and by age. These measures will be used to quantify the potential clinical utility of pre-emptive PGx testing in different settings, directly informing policy decisions around the implementation of PGx nationally.

In addition to the primary outcome, baseline characteristics will be presented. Medicine exposure by British National Formulary (BNF) class will be presented with sub-analysis by age group, sex, and the presence of recorded co-morbidities. Analysis will be presented for the whole cohort, and separately for inpatient and outpatient arms.

Genotype and metaboliser frequencies, derived using CPIC guidelines, will be presented for the whole cohort. These frequencies will then be analysed by age, sex, and ethnicity. Analysis will be presented for the whole cohort, and separately for inpatient and outpatient arms. Statistical differences in genotype based on demography, or recruiting site, will be tested via ANOVA or independent t-test. Genotype frequencies will be compared against an independent control cohort, generated as part of an ongoing trial, genotyping 1500 patients from the TARDIS Trial.[25] This will allow for comparison as to whether the dataset generated in this fellowship is consistent with others around the country, so clarifying generalisability.

Finally, the predictive value of patient variables, such age, co-morbid status, or ethnicity, for exposure to medicines where pharmacogenetic guidelines exist will be determined. This will be used to assess whether these variables, either in isolation or in combination, could be used to define a targeted screening approach for pharmacogenetics.

8. DATA COLLECTION, SOURCE DATA AND CONFIDENTIALITY

8.1. Data Collection at Recruitment

An online recruitment proforma will be completed for each participant by the study team, which will assign the participant with a unique study ID. This online proforma will be part of a bespoke electronic study tool, developed in the MCGM for this study by a web-developer (Mr Algy Taylor). This will provide the study team with access to an online recruitment portal. This online tool will be hosted on Manchester University NHS Foundation Trust Servers and will only be accessible within the trust via the intranet (Internally facing). The system builds on existing informatic architecture and will be subject to all legal requirements as outlined by the General Data Protection Regulation (GDPR) and set by the Medicines and Healthcare products Regulatory Agency (MHRA). Initially, the study team will be asked to collect the following details.

1. Name
2. Date of Birth

3. Sex
4. NHS Number
5. Recruiting site
6. Allergy status
7. Admission Date (IPTIP-I arm only)
8. Participant Reported Current Medicines (IPITIP-O arm only)

8.2. Sample Collection, Storage and Genotyping

The information gathered at recruitment will be sufficient for the electronic platform to generate a study ID, allowing 3ml of EDTA blood or 2ml of saliva to be taken and labelled with the IPTIP study ID only. Blood or saliva samples will then be transported to the Manchester Centre for Genomic Medicine via existing and secure clinical pathways for internal specimen transport. There, DNA will be extracted and quantified by the North West Genomic Laboratory Hub (NW-GLH), an NHS ISO15189 accredited laboratory. DNA samples will be labelled with the Study ID and stored at -20^{O}C until genotyping. Where DNA samples are available, an aliquot of DNA will be transferred from the DNA archive to the -20^{O}C study freezer and labeled with the Study ID only. If a saliva sample has been completed at home by the participant, it will be returned in a pre-printed freepost envelope marked UN3373 to the genetics research office, after which it will be labelled with IPTIP ID only and delivered to the NW-GLH laboratory for DNA extraction as detailed above. Where buccal samples are collected, these will be labeled with the patient's study ID after collection and transferred to the NW-GLH for storage (as above).

Genotyping will be undertaken using the Agena^{TM} iPLEX PGx 74 assay. This pre-designed assay targets frequent and clinically relevant variants across 20 pharmacogenes. This is a 3-well assay, but a 4th will be added for CYP2D6 copy number variants. To assess the analytical performance of the Agena^{TM} platform against other pharmacogenetic systems, a proportion of the samples will be tested in parallel on an additional pharmacogenetic platform. These additional platforms will not test variants other than those already on the Agena^{TM} iPLEX PGx 74 platform. With donor consent, anonymized samples will be kept beyond the completion of the study for future ethically approved

research. Buccal samples collected as an optional extra sample type for a sub-set of patients, will be disposed of at the end of the study, according to standard laboratory procedures.

Where the patients opt to provide a buccal sample [Amendment 3], this will be tested via the genedrive *CYP2C19* ID Kit (Genedrive Diagnostics Ltd). This system is able to detect common pharmacogenetic variation in the *CYP2C19* gene from a buccal swab.

8.3. Prescribing Data Collection and Analysis

Prescribing data for participants from the IPTIP-I arm will also be collected from the discharge summary and from the inpatient prescription chart. This data will be collected by the study team via a dedicated collection tool, also built into the bespoke portal. This can be done at a later timepoint, after recruitment.

Following source data collection, with participant consent, study ID, identifiable demographic, and inpatient prescribing data will be shared with Graphnet CareCentric who operate the Greater Manchester Care Record (GMCR). These records will then be linked with outpatient prescribing data from within the GMCR and deposited as a pseudonymised dataset (labeled with study ID only) available for analysis by the research team within Graphnet's secure data analysis environment. Participant genotype will be then be added to the final dataset within the secure research environment, linked by the Study ID. The final pseudonymised dataset will contain study ID, medicine history, participant genotype and metabolizer status.

The GMCR joins together Greater Manchester's different NHS and care organisations to support hospitals and other care services access individual health and care records quickly and securely. Utilization of the GMCR for the IPTIP trial offers several unique advantages. Firstly, the near 'real-time' data availability enables access to up-to-date prescribing data from the primary care setting in a more reliable and accurate way than is available in other data sources. The data source also provides access to the historical prescribing data of any participant registered with a GP in the conurbation. There is precedent for research and data-sharing such as this using the GMCR and the Graphnet environment. At the time of writing, 15 studies have been approved using GM Care Record Data (https://gmwearebettertogether.com/research-and-planning/). Previously published studies using the GMCR have not sought written consent from participants as the datasets were fully de-identified. Here, as this project first collects the data using the GMCR, extracts it into the Secure

Data Environment known as the Analytics and Data Science Platform (ADSP) to makes use of pseudonymised data for analysis, we will seek consent from participants for data sharing, handling and analysis within a secure environment.

There will be some infrequent cases where access to the GMCR is not possible for participants, either because the individual has chosen to opt-out of involvement in the GMCR or, more likely, because they are not registered with a GP in Greater Manchester. In these cases, the research team will seek permission from the participants to manually access historical prescribing data via the Summary Care Record (SCR). With a participant's permission, the SCR can be viewed through internal MFT clinical systems or through the Summary Care Record application (SCRa) on the Spine web portal. These data will then be uploaded, alongside the study ID into the final analysis dataset within the secure research environment.

A schematic representation of the data collection, access and analysis process for this project is given in Appendix 1.

The recruitment proforma, containing the "key" to de-anonymize the final dataset, will be stored securely by the senior investigator, Professor Bill Newman for 5 years following the end of the study. After this, the key will be destroyed, rendering the dataset fully anonymous. There is no formal study intervention and participants will not be contacted after the initial enrolment. No participant specific results will be generated and fed back to the participants or their clinician(s).

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Analysis

A Chi Square Test of Independence will be applied to assess whether the prevalence of actionable genotypes is the same in the IPTIP cohort as in existing control datasets (ie. TARDIS and Vanderbilt datasets).[24] The criterion for an actionable variant is as previously detailed (Section 7.0). The primary outcome measure between the IPTIP-I and IPTIP-O cohorts will be compared using the same statistical approach. Statistical differences in genotype based on demography, or recruiting site, will be tested via ANOVA or independent t-test. Logistic regression analysis will be used to determine the predictive value of patient variables, such age, co-morbid status, or ethnicity, for exposure medicines where pharmacogenetic guidelines exist. Statistical support will be provided throughout the trial by an independent trial statistician, Mr Duncan Stoddard.

9.2. Sample Size:

Sample Size: Determined based on the primary outcome and calculated with assistance from the NIHR Research Design Service and an independent statistician, Duncan Stoddard. 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=1.96 for 95% CI), P is expected true proportion, e is desired precision.

For the inpatient arm, a previous estimate from Vanderbilt, USA, suggests that 40% of patients had a genetic variant related to a medication that they were prescribed. Given the diversity of the population presenting to MFT and the relative over-medicalisation of healthcare in the USA, a lower prevalence of 0.3 will be chosen to represent P which, with a desired precision of 0.05 and a CI of 95%. This results in a required sample size of **323**.

For the outpatient arm, feasibility trials in Vanderbilt, USA, and the Netherlands suggest that approximately 30% of patients have a genetic variant which would impact prescribing of a medication they were actually prescribed.[26,27] Therefore, a P of 0.3 will again be used, assuming the same precision and CI as above, generating a required sample size of **323**.

10. DATA MONITORING AND QUALITY ASSURANCE

The study will be subject to the audit and research governance monitoring processes of the University of Manchester. In addition, an independent steering committee will be established who will be responsible for ensuring the fidelity of trial to the submitted protocol and will regularly review progress.

With participant consent (Section 6.3), anonymised study data and anonymised 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 anonymised to the external centre.

11. SAFETY CONSIDERATIONS AND ADVERSE EVENTS

The design and observational nature of this trial means that the risk of adverse events and safety concerns are small. The only procedure which has a small potential for harm is the blood sample

being taken to isolate DNA. All staff will be trained to take blood and recognise any complications of phlebotomy. Minor adverse events would include bleeding and bruising.

12. PEER REVIEW

This study protocol has been externally reviewed by a National Institute for Health Research (NIHR) panel. Based on this protocol, the study was approved with funding commencing on 1 October 2021.

13. ETHICAL and REGULATORY CONSIDERATIONS

13.1. Approvals

This study will be subject to ethical review by NHS Research Ethics Committee (REC) and 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.

13.2. Risks

Due to the design of the study, there are very few risks to participants and researchers.

1. There is a small risk of needlestick injury to the researcher, but all site staff taking blood will be properly trained. As such, the risk is not above that of normal clinical practice.

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

3. All participant DNA samples will be stored securely within an NHS facility which has extensive experience handing such samples and is ISO15189 accredited. As such, the risk of DNA contamination or loss is very low.

4. All identifiable participant data will be stored on a secure password protected servers, either within the NHS (Manchester University NHS Foundation Trust), within a secure Graphnet CareCentric environment or within the NHS GM's Analytics and Data Science Platform (ADSP). All these sites have experience running large trials involving the handling of datasets across Greater Manchester. Therefore, based on extensive experience, the risk of data loss or breach is very low. Confidentiality of data is a key consideration and therefore a decision has been made to pseudonymise the data. Complete de-identification would preclude follow up analysis, and therefore this has not been included in the protocol.

14. STATEMENT OF INDEMNITY

The University has insurance available in respect of research involving human subjects that provides cover for legal liabilities arising from its actions or those of its staff or supervised students. The University also has insurance available that provides compensation for non-negligent harm to research subjects occasioned in circumstances that are under the control of the University.

15. FUNDING and RESOURCES

The study has been fully funded by the National Institute for Health Research (NIHR) and study recruitment support has been approved by Clinical Research Network.

16. PUBLICATION POLICY

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 the PPIE VOCAL team.

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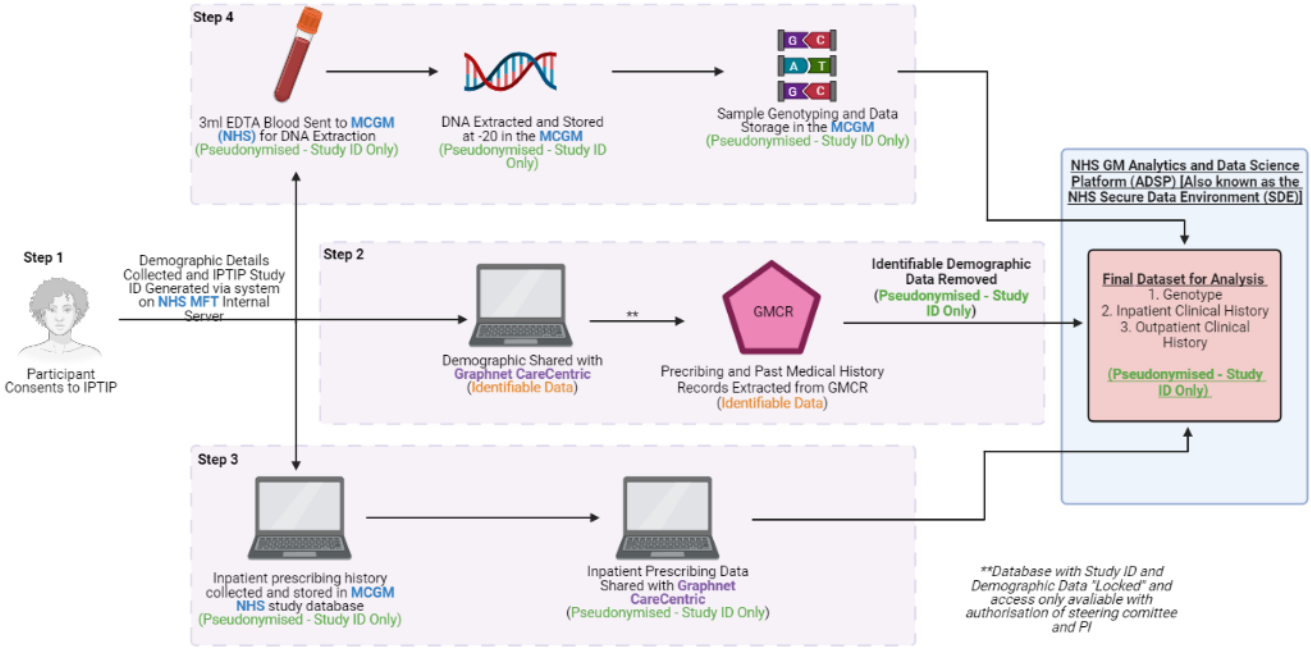
Appendix 1

Schematic representation of data collection, access, and analysis via NHS internal servers and Graphnet CareCentric.



Appendix 2 – Patient Facing Information on the Genomic Medicine Service Alliance Website (GMSA)

******START******

There is growing understanding that the effectiveness of many regularly prescribed medications can be influenced by relatively common genetic changes. Researchers in Manchester want to explore whether information about people's genetic information could be used by doctors when they are deciding what medication to prescribe.

- It's estimated that nearly 99% of people have genetic changes which could influence their response to a medicine.
- Many medicines need to be activated by specific chemicals in the body before they work. For example, around 10% of people don't respond well to codeine because their bodies don't activate the chemical that converts it into morphine to relieve pain

The Implementing Pharmacogenetics to Improve Prescribing (IPTIP) study has been launched at the Manchester University NHS Foundation Trust to help understand whether this testing would be useful in clinical practice.

If you're 18 years of age or over and have previously been seen as a patient at the Manchester University NHS Foundation Trust, you could be eligible to participate. Participants are asked to provide a blood or saliva sample and give permission for researchers to access their medical records. For more detailed information on the study, you can access the detailed Patient Information Leaflet **here.**

If after reading the patient information you're keen to find out more, you can contact the study team by emailing IPTIP@mft.nhs.uk.

******END******