HAPPY
Healthy Aging Pharmacogenomics and PolypharmacY

Study Title: HAPPY
Healthy Ageing Pharmacogenetics and PolypharmacY

Sponsor's Project Number: 100258
REC Reference Number: 21/PR/0673
IRAS ID: 295387

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CHIEF INVESTIGATOR (CI):

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Protocol amendment /Revision History

Protocol Version and Date	**New text**
0.4	Version for submission to IRAS
0.5	REC recommendations included
0.6	REC recommendations included

SPONSOR: Congenica Ltd

Funding Source:
Congenica Ltd
Innovate UK

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Statement

The Chief Investigator (CI) and the Sponsor representative have discussed this protocol version. The investigators agree to perform the investigations and to abide by this protocol except where departures from it are mutually agreed in writing.

The Investigator agrees to conduct the trial in compliance with the protocol, GCP, the Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005 2nd Edition), the Sponsor's SOPs, and other regulatory requirements as appropriate.

Chief Investigator Dr Suzanne Drury	Signature	Date

Acknowledgements and Protocol contributories

Dr Judith Hayward
Dr Imran Rafi
Dr Nick Lench

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1 List of abbreviations

CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
ICF	Informed Consent Form
ISF	Investigator Site File
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Participant Information Sheet
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee
PGx	Pharmacogenomics

2 Roles and Responsibilities

CHIEF INVESTIGATOR (CI):
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3 Study synopsis

Brief title:	HAPPY
Official title:	Health Aging Pharmacogenetics and PolypharmacY
Sponsor reference number:	100258
Public database identifier	**tbc
Study design	Case series/case note review; Feasibility/pilot study; Questionnaire, interview or observation study
Study Population/disease condition	Over 50 years old on multiple medications for cardiovascular disease, pain control, mental health and gastro protection.
Eligibility criteria:	***Inclusion criteria:*** • Over 50 years of age. • Taking 3 or more medicines. • The clinical areas we will focus on will include cardiovascular health, pain (musculoskeletal) gastro protection and mental health • Who agree to follow up after pharmacogenetics analysis.
	Exclusion criteria: • Who do not have the capacity to consent to take part in the project and • Who are suffering from terminal cancer or terminal disease • Pregnant • Suffering from severe mental illness • Under the age of 50 years • Are not able to understand English or translated material • Who do not agree to follow up after pharmacogenetics analysis and in particular those patients who have actionable pharmacogenetics.
Target number of participants	500 over 20 months

Criteria for evaluation	**Primary outcome measure(s)** Number of currently actionable DNA variants per patient. • The number of patients with currently actionable variants identified. • Rate of recommendations for prescription changes • The prescribing decisions made on receipt of the PGx data. • Factors contributing to whether recommendations are or are not converted to medication change within the medication review

	Secondary outcome measure(s) # and type of adverse effects reported by patients pre and post receipt of PGx data # Actionable PGx variants which do not impact on current medication Anxiety measures at baseline, 1 mth, 3 mths, 6 mths and 1 year after consent Patient acceptance of the use of PGx The time taken to process and receive DNA/PGx results from the time of consent to the project. Fraility index measures at baseline, 1 mth, 3 mths, 6 mths and 1 year after consent Service use review (eg. #hospital admissions, GP appointments and recorded adverse effects at baseline and 1 year)
Sources of funding	The trial is funded by Congenica Ltd and Innovate UK.
Anticipated start date:	September 2021
Anticipated primary completion date:	April 2023
Sponsor	Congenica
Key Contact names	Chief Investigator: Dr Suzanne Drury Email: suzanne.drury@congenica.com Tel: 01223 499965 Fax: n/a Sponsor representative: nick.lench@congenica.com

4 Background

Polypharmacy, the use of multiple medications (3 or more) at the same time is common amongst older individuals and/or in people with multiple co-morbidities. In these populations, medicines are frequently associated with adverse drug reactions (ADRs), falls risk and may have a negative impact on both cognition and quality of life. There are an estimated 237M medication errors per year in the NHS (England), with 66M of these potentially clinically significant.

"Definitely avoidable" adverse drug reactions collectively cost ~£100M annually, contribute to ~1700 deaths/year and are directly responsible for an additional ~700 deaths/year. Evidence demonstrates that over 40% of ADR-related hospital admissions may be preventable.

Pharmacogenomics (PGx), the study of how genes affect an individual's response to drugs, aims to provide information to improve safety and effectiveness of drug treatment. Pharmacogenomic information can be considered actionable if it leads to a change in prescribing decisions, such as alternative medications or dosing. PGx has been shown to be effective for preventing potential side effects of polypharmacy. As a strategy for optimizing medication usage, PGx is becoming an important element of precision medicine with significant potential impact in older people with polypharmacy.

This research study aims to investigate the use of a PGx-led approach to the management of polypharmacy. The aim is to assess outcomes e.g., actionable PGx DNA sequence variants, de-prescribing, reduced ADRs and effect on number and length of hospital admissions and General Practice (GP) visits.

5 Study objectives

5.1 Primary objective

The use of innovative technology, scientific and clinical expertise available through this programme of work will enable us to study and understand how we can use genetic data in day-to-day clinical General Practice. This particularly applies to those patients with complicated medical problems and includes patients on multiple drug treatment treating long term medical conditions such as diabetes and cardiovascular disease. PGx is the study of how genes affect an individual's response to drugs and aims to provide information to improve safety and effectiveness of drug treatment. If we can identify those patients who are at risk of adverse drug effects by virtue of their genetic make up then we may be able to pre-emptively prescribe at doses that take into account genetic information with clinical prescribing protocols and thus reduce side effects.

There is a paucity of studies that have assessed implementation of pharmacogenomics in primary care and its implementation in association with polypharmacy. The principle of using information on gene variants that lead to new actionable clinical management is important clinically and may provide information that leads to patient safety through reduction of adverse drug effects. However the implementation and use of pharmacogenomic information in clinical General Practice in the NHS requires integration with current workflows including the recording of pharmacogenomic data on clinical decision support systems, be readily available and require relationship based, shared decision making care.
This innovative study brings together the scientific analysis of genetics relating to commonly

prescribed drugs used in the clinical areas of cardiovascular disease, pain control, mental health and gastro protection.

5.2 Secondary objectives

If the first research question is how do we generate pharmacogenomic data and integrate it with current workflows and data recording in clinical general practice then the next question is how we measure the effect of using pharmacogenomic data. There is a need to use established techniques including patient questionnaire .
Participants can optionally consent for use of data in future health research projects, and for validation and improvement of diagnostic testing methods.

6 Trial design

Case series/case note review; Feasibility/pilot study; Questionnaire, interview or observation study

7 Participation selection criteria

There will be no exceptions (waivers) to eligibility criteria prior to participant inclusion into the study. Any questions raised about eligibility should be addressed prior to entering the participant.

The eligibility criteria have been carefully considered and are standards used to ensure the trial results can be appropriately used to make future decisions for other people with similar disease or medical condition. It is therefore vital that exceptions are not made to thefollowing detailed selection criteria.

Participants will be considered eligible for enrolment into this study if they fulfil the inclusion criteria and none of the exclusion criteria as defined below.

Eligible participants will be assigned a Trial specific Identification number in a pre-agreed format in accordance with Site Identifier and next sequential numerical value, e.g. PGx_Ban_001.

7.1 Inclusion criteria

- Over 50 years of age.
- Taking 3 or more medications for cardiovascular health, pain (musculoskeletal) gastro protection and mental health
- Agree to follow up after pharmacogenetics analysis.

7.2 Exclusion criteria

- Do not have the capacity to consent to take part in the project
- Suffering from terminal cancer or terminal disease.
- Pregnant
- Suffering from severe mental illness.
- Under the age of 50 years.
- Not able to understand English or translated material
- Do not agree to follow up after pharmacogenetics analysis and in particular those patients who have actionable pharmacogenetics.

8 Participant Recruitment process

Patient recruitment will commence only once there is evidence that the following approval/essential documents are in place:

1. REC and HRA approval

2. Final sponsorship and host site confirmation

All subjects who wish to enter the study will be fully screened and consented appropriate delegate of the Chief Investigator.

Potential participants will be identified by two participating General Practices based on the inclusion criteria. The practices use EMIS and SystmOne electronic health record (EHR) systems. Searches across the databases are a routine part of clinical General Practice and practice staff who provide direct care team in the practices who have expertise in data searches will identify potential participants across the 4 chosen clinical areas.

The study will be conducted by the sponsor, participating sites and all investigators in accordance with the protocol, the Declaration of Helsinki, the guidelines on Good Clinical Practice (GCP) and all legal requirements, including applicable national legislation, for the conduct of this study.

9 Study procedures

9.1 Informed consent

It is essential that all trial teams undertaking the informed consent process have signed the Sponsor's Delegation of Responsibilities Log to ensure that the person has been delegated the responsibility by the study CI/PI.

Informed consent will be obtained from eligible participants by a member of the research team after confirming the eligibility, inclusion and exclusion criteria.

The Principal Investigator or designee will explain to the participant that they are under no obligation to enter the trial and can withdraw at any time during the trial, without having to give a reason. Those who agree to take part will be asked to sign a Consent Form prior to any study investigation or treatment.

A copy of the signed Informed Consent Form (ICF) along with a copy of the most recent approved Patient Information Sheet (PIS) will be given to the study participants. An original signed & dated ICF will be retained.Consent will be documented in the OpenApp study registry.

If new information results in significant changes to the risk-benefit assessment, the ICF will be reviewed and updated as necessary. All participants, including those already enrolled in the study, will be informed of the new information, given a copy of the revised ICF and askedto re-consent if they choose to continue in the study.

9.2 Randomisation procedure

There is no need for randomisation in this study.

9.3 Discontinuation/withdrawal of participants and stopping rules

In consenting to the study, participants are consenting to a saliva sample. However, an individual may withdraw from the study for anyone of the following reasons:

Intercurrent illness that prevents further protocol treatment

Any change in participant's condition that in the investigator's opinion justifies discontinuation.

Withdrawal of consent by the participant

As participation in the study is entirely voluntary, the participants may choose to discontinue involvement at any time without penalty or loss of benefits to which they may be entitled. Although not obliged to give a reason for discontinuing their participation, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participants' rights. Participants who discontinue study participation for any of the above reasons should remain in the study for the purpose of follow-up and data analysis.

9.4 Definition of the End of Trial

The study will be completed at the receipt of the sample of the last recruited patient, or at the end of 20 months. The REC and the Sponsor will be notified of the end of study within 90 days of its planned completion or within 15 days if the study is terminated early.

10 Study Procedures

10.1 Patient selection

Patients who are over 50 years of age taking 3 or more medicines will be identified through searches of practice disease registers. Other ways of identifying these patients will be at the time of medication reviews and engagement with primary care practitioners in General Practice across the two sites who will be informed about the study and its purpose. We will focus initially on patients on medication for cardiovascular disease, mental health, pain and gastroprotection.

10.2 Questionnaire

Information on patients adverse reactions will be gathered in the form of review of patient records by their GP and questionnaires at multiple timepoints throughout the study; pre-PGx report, 1 month, 3 month, 6 month and 12 month post-medication review (see appendix 1). This will include capture of data on number of GP visits, medication use, hospital admissions, adverse drug reactions.

10.3 Sample processing

Samples relating to the study will be assigned a unique study identifier. A saliva sample will be sent to a GCP lab for germline DNA extraction. DNA will be processed using the Illumina Global Diversity Array. Raw data will be transferred to Congenica Ltd (UK) via secure sftp. Raw genetic data will be processed by Congenica into genotype data. Genotype data will be processed to a pharmacogenomic report (PGx) by Abomix (Finland) and returned to Congenica Ltd and subsequently the patients GP (see appendix 2). Participant samples will be held, managed, and disposed of in compliance to HTA regulations. DNA which has not been consented for further research will be destroyed at the end of the study. DNA which has been consented for further research will be destroyed no more than 10 years after the end of the study.

10.4 Data collection

Information from the questionnaire will be collected at the designated timepoints and captured in a customized OpenApp study registry.

10. 5 Management review

Phamacogenetic data from the patient will be used to suggest changes to prescribing within the confines of the authorization, based on guidelines from CPIC, DPWG and FDA and in the context of the patient history. The clinical decision for prescribing for each patient is however the physician's responsibility.

11 Patient journey and study flow chart

Please refer to Appendix 2/3.

12 Safety Events

This study uses medications with a marketing authorization in the UK, prescribed in accordance with the terms of that authorization and FDA labelling. Pharmacogenetic data from the patient will be used to suggest changes to prescribing within the confines of the authorization, NHS prescribing practices and NHS medication availability, based on guidelines from CPIC and DWPG, and in the context of the patient history. The clinical decision for prescribing for each patient is however the physicians responsibility.

a. Definitions

Adverse Event (AE)—any untoward medical occurrence in a participant whether it is considered to be related to the procedure or not, that includes a clinical sign, symptom, or condition and/or an observation of a near incident. This does not include pre-existing conditions recorded as such at baseline; continuous persistent disease or a symptom present at baseline that worsens following the procedure.

Serious Adverse Event (SAE) - any Adverse Event or untoward medical occurrence in a study participant that can be wholly or partly due to the procedure which resulted in any of the following:

- Death
- Is life-threatening (places the participant, in the view of the Investigator, at immediate risk of death)
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if it is a precautionary measure for observation, including hospitalisation for an electiveprocedure for a pre-existing condition)
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions)
- Consists of a congenital anomaly or birth defect (in offspring of participants regardless of time of diagnosis)
- Is another important medical condition

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or require intervention to prevent one of the outcomes listed in the definition of serious AE will also be considered serious.

b. Recording Adverse Events (AEs)

All Adverse Events will be recorded in the general practice notes in the first instance.

A record of all AEs, whether related or unrelated to the treatment, will also be kept in the CRF and the Sponsor's AE Log.

c. Investigator Responsibilities relating to Safety Reporting

Collection, recording and reporting of AEs (including serious and non-serious events and reactions) to the Sponsor will be done according to the Sponsor's Safety reporting for non-CTIMP studies .

All SAEs will be recorded in the GP notes and the CRF, and the Sponsor's AE Recording Log. The AE Log will be sent to the Sponsor on request and every 3 months.

All SAEs will be reported both to the Sponsor & REC using the SAE report form for research other than CTIMPs (non-CTIMPs) published on the HRA website.

The Chief or Principal Investigator, or a member of the research team, at any participating site will complete the SAE form which will be e-mailed to quality@congenica.com within 48hrs of the Investigator becoming aware of the event, and via email to the relevant REC.

The Chief or Principal Investigator will respond to any SAE queries raised by the Sponsor as soon as possible. Follow-up reports must continually be completed within an acceptable time-frame and sent as detailed above until the reportable event is considered resolved.

Events will be followed up until resolution; any appropriate follow-up information will be clearly marked as such and reported to the sponsor as above in a timely manner.

Full reports should be completed and submitted to REC within 15 days of the event.

d. Notification of deaths

Only deaths that are assessed to be caused by the study procedures will be reported to the Sponsor. This report will be immediate.

13 Data management and quality assurance

a. Confidentiality

All data will be handled in accordance with the current Data Protection laws.

The samples and questionnaire will not bear the participant's name or other directly identifiable data. The participant's trial Identification Number (ID) only will be used foridentification. The primary care EHR can be used to cross reference participants' identifiable information.

b. Data collection tool

Questionnaire data will be collected in the OpenApp study registry. Patients will be offered support to complete the questionnaire by their practice.

c. Incidental Findings

All subjects will be informed in a timely manner, both verbally and in writing, of any new information, findings or changes to the way the research will be conducted that are of potential relevance for participants and might influence their willingness to continue in this study.

d. Data handling and analysis

Only the approved members of the GP surgery will have access to patient identifiable information. Each sample sent for testing will be assigned a study ID to ensure anonymity (pseudonymised). Patient identifiable information will be needed to match questionnaire and medication information with the study samples. This information will be stored on an encrypted, password protected database. Patient identifiers to the study will be held in the same clinical (EmMIS/SystemOne) EHR in the same way information is recorded for the patient population.

Raw genomic data will be generated in a laboratory compliant with GLP and data deleted after a specified time period after transfer for processing by Congenica.

Data at Congenica will be managed, stored and processed according to Congenica's security and data management policies. Congenica is certified to ISO27001:2017 and as such has matured data and information security management processes in place. The company is committed to the confidentiality of personal information and its responsibilities with regard to disclosure of such information. The company has roles of Caldicott Guardian (Chief Scientific Officer) and Senior Information Risk Owner (Quality Assurance and Regulatory Affairs Manager) as these are legal requirements for NHS governance. The Chief Executive Officer is responsible for ensuring that Congenica complies with the pseudonymisation requirements as set out in client contracts. The Quality Assurance and Regulatory Affairs Manager is responsible for ensuring this policy is up to date and complies with current legislation and regulations. All employees, contractors and associates share the responsibility for ensuring that personal identifiable information is handled in accordance with this policy and are trained appropriately to do so. Any changes to policy are communicated to all staff and their acceptance acknowledged in individual training records. Confluence and JIRA systems are used to manage policies, SOPs, work documents etc and perform risk assessment.

Congenica have a quality management system in place (ISO13485:2016) and has Information Governance/NHS Digitial (organisations which have access to NHS patient data and systems must undergo self-assessment to provide assurance that they are practising good data security and that personal information is handled correctly. In addition, Congenica has Cyber Essential certification. Data will have restricted access and only be accessible by authorised individual's that require access to work on the project.

Genomics data is stored in Amazon Web Services, which also holds ISO27001:2013 accreditation. All suppliers to Congenica, including services such as AWS, are reviewed prior to purchasing, following a supplier approval process, where any potential risks to the quality standards in place by Congenica by using the supplier are measured and mitigation put in place. All suppliers are reviewed on an annual basis.

Genomic data for pharmacogenomic reports will be processed by Abomix. Abomix operate under an ISO 13485 quality system but we are not currently accredited by a third party. The software we use for the PGx Interpretation Service is classified as an internal software for producing a service under Finnish legislation (http://www.finlex.fi/data/normit/39643-maarays_2_2010_laiterekis teri_ilmoitus.pdf) which is under the supervision of Valvira the National Supervisory Authority for Welfare and Health.

Metadata and pseudonymised reports will be stored in a customised OpenApp registry. OpenApp are currently undergoing ISO27001 (Information Security Management) and have been implemented as a patient registry of choice for multiple studies, including European Reference Networks for rare disease. OpenApp follow the anonymisation code of practice as published by the

UK Information Commissioner in 2021.

14 Archiving arrangements

Genomics data (pseudonymsed) will be stored in Amazon Web Services, which also holds ISO27001:2013 accreditation. Pseudonymsed metadata collected from the study will also be held on AWS after the end of the study. The sponsor and general practicioners recruiting to the study will have access to this pseudonymsed data.

The agreed archiving period for this trial will be 10 years.

15 Statistical design

a. Endpoints

15.1.1 Primary endpoints

The number of patients with currently actionable variants identified.
• Rate of recommendations for prescription changes
• The prescribing decisions made on receipt of the Pgx data.
• Factors contributing to whether recommendations are or are not converted to medication change within the medication review.

15.1.2 Secondary endpoints

and type of adverse effects reported by patients pre and post receipt of PGx data
Actionable PGx variants which do not impact on current medication
Anxiety measures at baseline, 1 mth, 3 mths, 6 mths and 1 year after consent
Patient acceptance of the use of PGx
The time taken to process and receive DNA/PGx results from the time of consent to the project.
Fraility index measures at baseline, 1 mth, 3 mths, 6 mths and 1 year after consent
Service use review (eg. #hospital admissions, GP appointments and recorded adverse effects at baseline and 1 year)

b. Sample size calculation

We aim to recruit 500 families over the course of 15 months at two sites. This is a realistic number of eligible cases based on inclusion criteria. By the end of this time we will have enough proof-of-principle data to enable design and execution of an appropriately powered clinical study.

c. Statistical analysis plan

Statistical analysis is not required for this study.

16 Ethics and Research Governance requirements

Before the site can enrol patients into the study, the Principal Investigator must ensure that written permission to proceed has been granted in compliance with the protocol as agreed by the Sponsor and which was accepted by the Research Ethics Committee (REC).

It is the responsibility of the CI to ensure that all subsequent amendments gain the necessary approval.

Within 90 days after the end of the study, the CI and Sponsor will ensure that the REC is notified that the study has finished. If the study is terminated prematurely, those reports will be made within 15 days after the end of the study

The CI will supply an End of Study report of the clinical trial to the REC within one year after the end of the trial.

a. Direct access to source data

The Investigator(s)/institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

17 Finance

The trial is funded by Innovate UK and Congenica Ltd, a leading provider of clinical decision support software andservices who have developed the gold-standard platform, Congenica, for analysis, interpretation and generation of clinically actionable reports on patient derived genomic data.

18 Insurance and indemnity

Congenica is the sponsor for this study and will provide indemnity to meet the potential legal liability of the sponsor harm to participants arising from the management of the research and design of the research.

NHS indemnity scheme will apply to the NHS investigators in the design of research and conduct of research. NHS bodies are liable for clinical negligence and other negligent harm to individuals coveredby their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate.

19 Development policy

The sponsor, participating sites and all investigators involved in the study shall treat all information and data related to the study as confidential and with the proper respect for the privacy of each participant. The parties shall equally warrant to not disclose such information to third parties or disclose such publicly, but shall use such information solely for the purpose of this study. All data shall be coded or de-identified prior to transfer of such data to sponsor.

The participating site and their proper investigators warrant that they shall not perform the study without having obtained the proper, written informed consent from each participant, in accordance with applicable legislation and as approved by the appropriate ethics committee/review board.

20 Publication policy

Publication: “Any activity that discloses, outside of the circle of study investigators, any final or interim data or results of the study, or any details of the study methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations.”

All scientific contributors to the study have a responsibility to ensure that results of scientific interest arising from study are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the study in a transparent and unbiased manner without consideration to commercial objectives.

To maximise the impact and scientific validity of the study, data shall be consolidated over the duration of the study, reviewed internally among all investigators and not be submitted for publication prematurely.

a. Before the official completion of the Study

All publications during this period are subject to permission by the Sponsor. If an investigator wishes to publish a sub-set of data without permission of the Sponsor during this period, the steering committee shall have the final say.

b. Up to 180 days after the official completion of the Study

During this period the Chief Investigator shall liaise with all investigators and strive to consolidate data and results, then submit a manuscript for peer review with a view to publication in a reputable academic journal or similar outlet as the Main Publication.

i. The Chief Investigator shall be senior and corresponding author of the Main Publication.

ii. Insofar as is compatible with the policies of the publication outlet and good academic practice, the other Investigators shall be listed in alphabetic order.

iii. Providers of analytical or technical services shall be acknowledged, but will be listed as co-authors only if their services were provided in a non-routine manner as part ofa scientific collaboration.

iv. Members of the Steering Group shall be acknowledged as co-authors only if they also contributed in other capacities.

v. If there are disagreements about the substance, content, style, conclusions, or author list of the Main Publication, the Chief Investigator shall ask the Steering Group to arbitrate.

c. Beyond 180 days after the official completion of the Trial

After the Main Publication or after 180 days from study end date, any Investigator or groupof investigators may prepare further publications. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be

submitted to the Sponsor for review at least sixty (60) days prior to submission for publication, public dissemination, or review by a publication committee. Sponsor's reasonable comments shall be reflected. All publications related to the study shall credit the Chief and Co-Investigators as co-authors where this would be in accordance with normal academic practice and shall acknowledge the Sponsor and the Funders.

21 Statement of Compliance

The study will be conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of the country in which the study site is located, including but not limited to the Human Rights Act 1998, the Data Protection Act 1998, the Human Medicines Regulations 2012, ICH GCP**,** the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the NHS Research Governance Framework for Health and Social Care (Version 2, April 2005).

This study will be conducted in compliance with the protocol approved by the REC and according to GCP standards. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and REC except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the Sponsor and REC as soon as possible.

22 List of Protocol appendices

Appendix 1 Questionnaire

Appendix 2 Flow chart

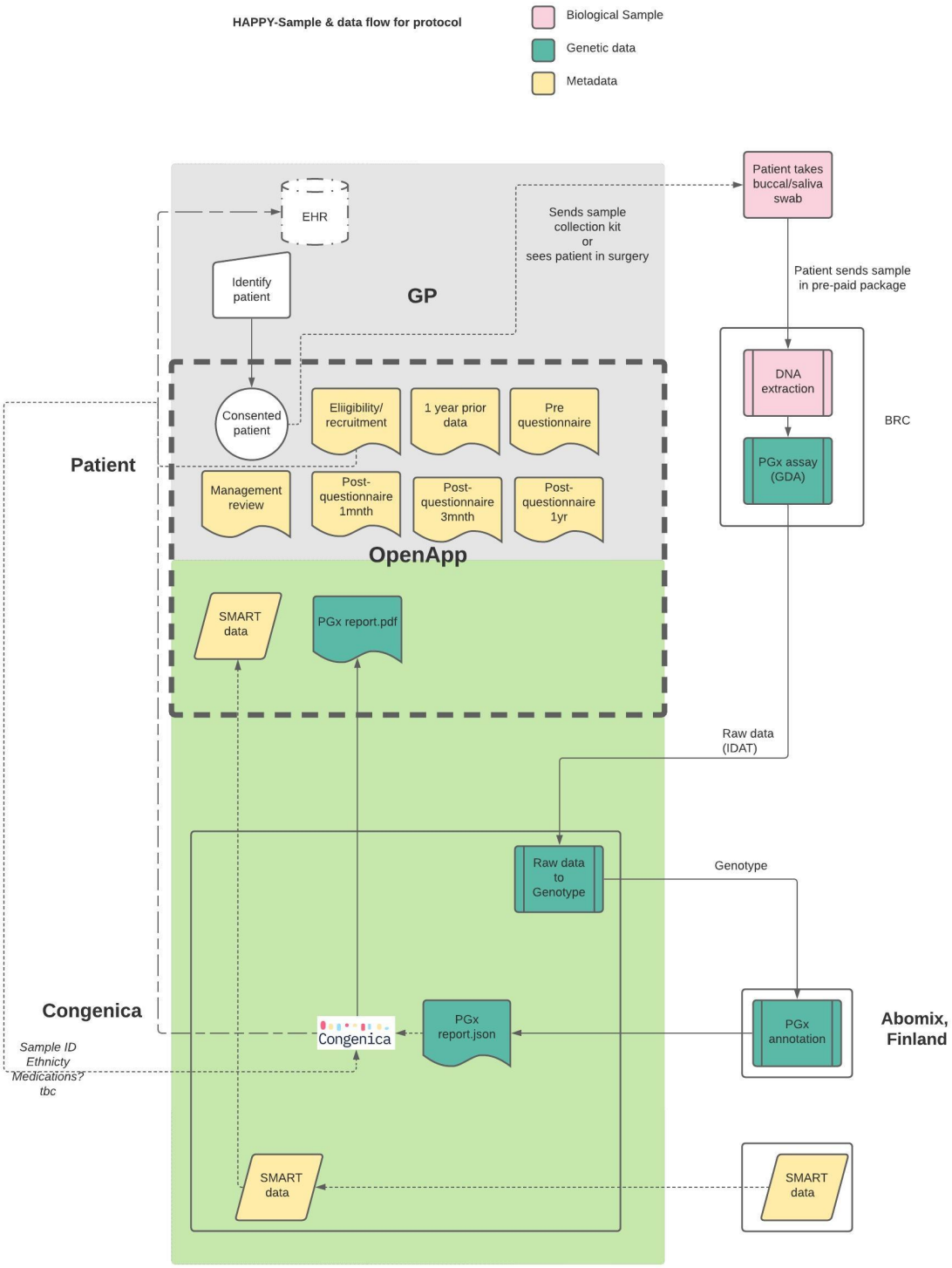
Appendix 3 Patient journey

Appendix 1

See file ‘HAPPY protocol v1.3 Appendix 3.xlsx’

Appendix 2

Study flow chart


HAPPY-Sample & data flow for protocol
Biological Sample
Genetic data
Metadata
Patient takes buccal/saliva swab
EHR
Sends sample collection kit or sees patient in surgery
Patient sends sample in pre-paid package
Identify patient
GP
DNA extraction
PGx assay (GDA)
BRC
Consented patient
Eligibility/ recruitment
1 year prior data
Pre questionnaire
Patient
Management review
Post-questionnaire 1mnth
Post-questionnaire 3mnth
Post-questionnaire 1yr
OpenApp
SMART data
PGx report.pdf
Raw data (IDAT)
Raw data to Genotype
Genotype
Congenica
Congenica
PGx report.json
PGx annotation
Abomix, Finland
Sample ID
Ethnicty
Medications?
tbc
SMART data
SMART data

Appendix 3

Patient journey