FULL/LONG TITLE OF THE STUDY:
REalist Synthesis Of non-pharmacologicaL interVEntions for antipsychotic-induced weight gain (RESOLVE) in people living with Severe Mental Illness (SMI)

SHORT STUDY TITLE:
Antipsychotics weight gain SMI

PROTOCOL VERSION NUMBER AND DATE:
V1.4;16th December 2022
This protocol has regard for the HRA guidance

RESEARCH REFERENCE NUMBERS

IRAS Number:	304370
SPONSORS Number:	AU-010-2021-IM
FUNDERS Number:	NIHR131871

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator 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 conditions of approval, 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 publically 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.

For and on behalf of the Study Sponsor:

Signature:
.....

Date:
...../...../.....

Name (please print):
.....

Position:
.....

Chief Investigator:

Signature: ..... I R Maidment .....

Date:
16/12/2022

Name: (please print):

.....Professor Ian Maidment.....

LIST of CONTENTS

KEY STUDY CONTACTS

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STUDY SUMMARY

Study Title	REalist Synthesis Of non-pharmacologicaL interVEntions for antipsychotic-induced weight gain (RESOLVE) in people living with Severe Mental Illness (SMI)
Internal ref. no. (or short title)	RESOLVE
Study Design	Realist synthesis (secondary data analysis and interviews).
Study Participants	People living with SMI (schizophrenia, schizoaffective disorder, bipolar disorder and all other non-organic psychoses) Taking or experience of taking antipsychotics (British National Formulary [BNF] 18, Chapter 4; section 3.6). Informal (family) carers for people with SMI taking or experience of taking antipsychotics Practitioners / informal carers supporting people with SMI taking or experience of taking antipsychotics
Planned Size of Sample	Sample size: Up to 30 service users and informal carers, and 20 practitioners, or until data saturation is reached.
Research Question/Aim(s)	To use realist synthesis, including primary data collection, to develop a framework and guidance for non-pharmacological interventions to manage

	antipsychotic-induced weight gain in people with severe mental illness (SMI).

ROLE OF STUDY SPONSOR AND FUNDER

RESOLVE represents independent research funded by the NIHR. Any changes in the protocol will agreed with the funders. The sponsor (Aston University, an academic institution) will assume overall responsibility for the initiation and management of the study, and will ensure that appropriate ethical and regulatory approvals are obtained as applicable.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/ GROUPS & INDIVIDUALS

Project Management Team (PrMT)

In summary, the PrMT will be responsible for running all aspects of the project and dissemination of results.

The PrMT main roles are:
1. To monitor the data and make recommendations on the initial programme theory and subsequent iterations.
2. To provide advice on relevant documents and the search strategy.
3. To provide advice on the guidance produced.
4. To monitor the research against time and target.
5. To support recruitment of participants for the qualitative interviews.
6. To provide support, mentorship and supervision to the Research Associate (and Chief Investigator) within their areas of their expertise.
7. To support dissemination of the results and wider knowledge mobilisation.

Composition of the PrMT
1. The Chief Investigator
2. The Research Associate
3. All co-applicants
4. Two to three service users with relevant direct experience.

PrMT meetings
1. The team will meet up every one to two months via video-conferencing and as required for additional meetings.
2. There will also be two key meetings: an initial meeting at the beginning of the project and a second around month 20.
3. Responsibility for calling the meetings lies with the Chief Investigator in association with the Research Associate.
4. Minutes of the meetings will be sent to all members, the sponsor and the funders.

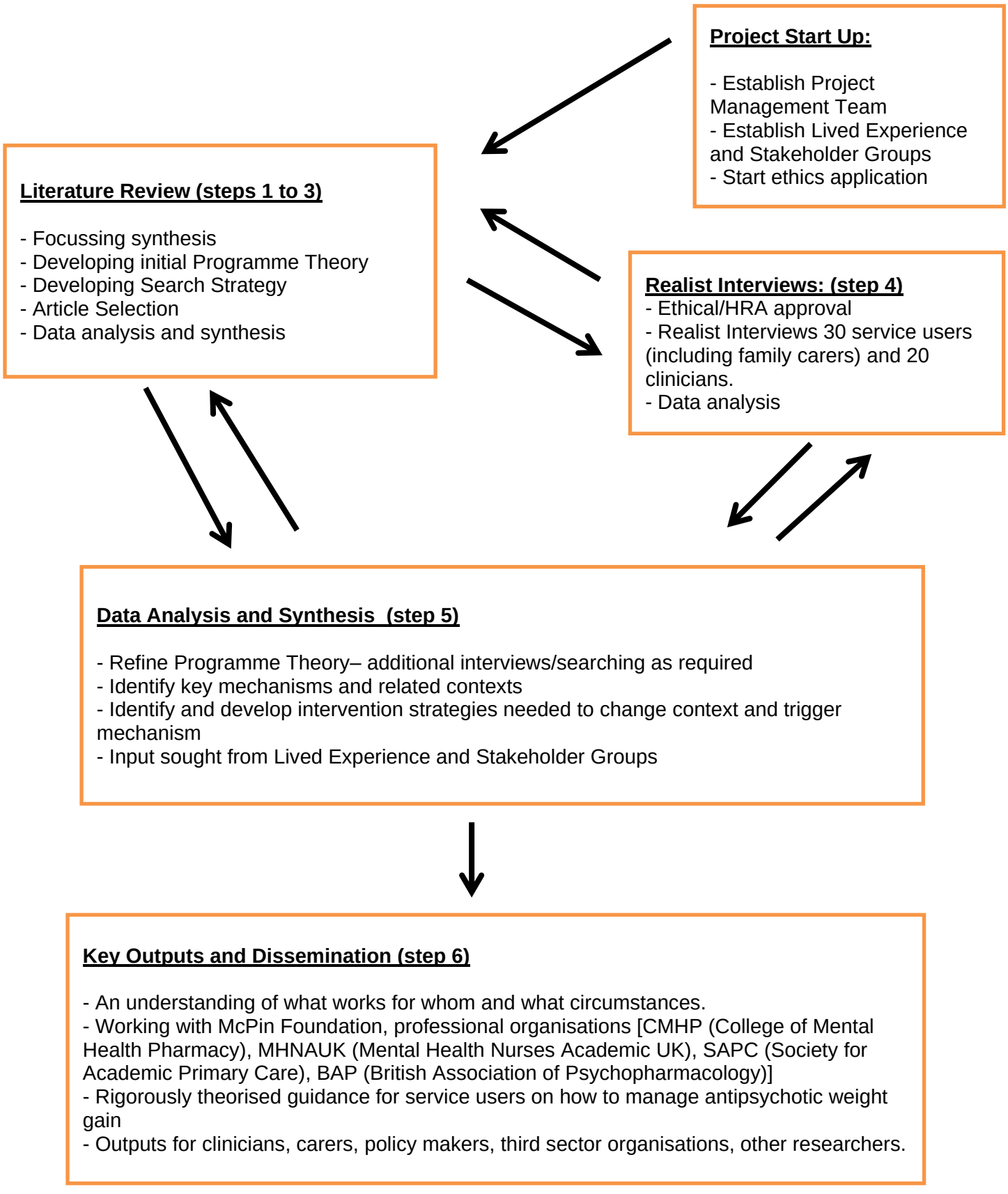
The PrMT will be supported by a **Lived Experience Group (LEG)** containing service users, family (informal) carers, and a **Stakeholder Group (SG)** containing clinicians and PrMT members.

1. Lived Experience Group (LEG) will contain approximately eight to ten service users and four family carers recruited via the McPin Foundation and other links. It will be chaired by Dan Robotham. The group will have face-to-face meetings (or if required due to COVID restrictions videoconferences) every 3 to 4 months. Meetings will be held at critical times including (for example) at the start of RESOLVE, once an initial draft of the guidance has been produced, and at the end of the project. The research will be conducted in partnership with the group, who will advise on design, study documentation, management and analysis, and support dissemination.

2. Stakeholder Group (SG). This will contain all co-applicants and other clinicians including members identified from professional links. The SG will provide feedback on the veracity of our programme theory, as it is developed during the project, monitor progress against milestones, promote the project, and communicate with all other stakeholders. A key role for the SG will be to help us to refine our dissemination strategy and to support the pathway to impact.

KEY WORDS: Antipsychotics, weight gain, severe mental illness, realist research.

STUDY FLOW CHART



STUDY PROTOCOL

REalist Synthesis Of non-pharmacologicaL interVEntions for antipsychotic-induced weight gain (RESOLVE) in people living with Severe Mental Illness (SMI)

1 BACKGROUND

Antipsychotics are widely used in the treatment of schizophrenia and other severe mental illnesses (SMI). Over the last 25 years, older drugs such as haloperidol (1st generation antipsychotics) have been replaced by newer 2nd generation antipsychotics (e.g. olanzapine). Second generation antipsychotics have fewer extrapyramidal (movement) side effects, but can cause significant weight gain, and diabetes is common (1). Clozapine, which is uniquely effective with no alternative treatment, is one of the worst culprits.

There are over 220,000 people being treated for schizophrenia in the UK at any one point in time (2). Up to 80% of people with schizophrenia or bipolar disorder are overweight or obese (3). One of the main causes is the side-effects of antipsychotics, with weight gains of up to 33.4 kg reported (4). This weight gain has devastating consequences: life expectancy is reduced by 20 years in people with schizophrenia, partly related to the consequences of this weight gain (5). A high Body Mass Index (BMI >40) is also a risk factor for poor COVID-19 outcomes, and schizophrenia itself a significant risk factor for mortality with COVID, even after controlling for co-morbidities such as BMI and diabetes (6).

The mental and physical health of people with SMI is a priority in the NHS Long-term Plan (7). The NHS Mental Health Implementation Plan identified the need for new models of care to address the physical health needs of people with SMI (8). Many different interventions have been tried to limit antipsychotic-induced weight gain, but there is not a clear picture of what works, for whom and in what circumstances. For example, the recent STEPWISE trial of structured lifestyle changes was unable to establish either clinical or cost-effectiveness due the complexity of the area and the need for an individualised approach (9) (10). Robust RCTs are challenging due to external confounding factors; there is also a high risk of bias.

2 RATIONALE

In RESOLVE, realist synthesis, combining primary and secondary data collection, will be used to understand and explain how, why, for whom, and in what contexts non-pharmacological interventions help service users to manage antipsychotic-induced weight gain. This approach is based on that successfully used to understand medication management in older people on complex regimens (11) (12).

Much work in this area is likely to be service evaluation type data or reports which may not be included in standard systematic reviews, but can be included in RESOLVE (13) (14). The interviews are needed to generate the qualitative data on the lived experience of weight gain and what works from a diverse group of service users (and practitioners). Thus, RESOLVE will directly address this deficit in the current literature, develop explanatory data and evidence-based guidance.

3 RESEARCH QUESTION/AIM(S)

Aim: To use realist synthesis, including primary data collection, to develop a framework and guidance for non-pharmacological interventions to manage antipsychotic-induced weight gain in people with severe mental illness (SMI).

4 OBJECTIVES

1. To understand how and why non-pharmacological interventions to manage antipsychotic-induced weight gain work (or not) for particular groups of people with SMI, in certain circumstances including in ethnic minority and other marginalised groups.

2. To synthesize the findings from objective 1 into a realist programme theory for interventions to manage antipsychotic-induced weight gain in people with SMI.

3. To use the realist programme theory developed from objective 2 to inform the development of guidance on managing antipsychotic-induced weight gain and a framework for intervention design.

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

Design: Two sources of data: secondary (literature review strand) and primary (interview strand) will be used to develop and test (confirm, refute or refine) the programme theory. A realist logic of analysis will be used to analyse and synthesise the data both within and across the two strands of this project. Engagement with clinicians and service users will be integral throughout the realist synthesis and supported by a Lived Experience Group (LEG) containing service users and family carers and a Stakeholder Group (SG) containing practitioners/clinicians.

The secondary data employed will include both published research studies and "grey" literature", such as service evaluations. Interviews will enable the direct involvement of a purposefully selected diverse group of service users and their carers, so that people with lived experience are directly involved in refining the programme theory on which the guidance will be based.

A five-step approach based on methods successfully used by the lead applicant in MEMORABLE will deliver the research (11).

1. Developing the initial programme theory

An initial (candidate) programme theory, which sets out how and why outcomes occur within an intervention (15) will be developed based on the collective experience of the project team with input from the LEG and SG. The initial programme theory will be mapped out as a series of steps required to reach the final desired outcome, identifying intermediate outcomes that take place either sequentially or in parallel. As the project develops, for each step, the relevant and associated context and mechanism for each outcome will be developed from data identified within included documents.

2. Developing the search strategy

The initial theory will be refined using secondary data. The need to find relevant data to develop the programme theory will guide searching. Search strategies will be developed and refined with input from the LEG and SG. The search strategies employed to identify relevant literature will be developed iteratively, and re-visited at predetermined milestones, using different permutations and additional concepts (16) (17).

The proposed initial sampling frame will be:

- **C**ontext: people living with SMI, taking antipsychotics, different types of SMI, different living homes/living environments, dual diagnosis including SMI and intellectual disability.
- **I**ntervention: non-pharmacological interventions including exercise and dietary interventions.

- **M**echanisms: triggered by the intervention, to be identified from the programme theory.
- **O**utcomes: weight, metabolic adverse events, quality of life, adherence, burden, economic. Unanticipated or unintended outcomes and outcomes considered important by LEG and SG.

Based on previous work (18) (19) (11) (26) (20) and international guidance (21) sources will include: MEDLINE/PubMed, Embase, Scopus, Web of Science (Core Collection), the Cochrane Library, CINAHL, PsycINFO, Sociological Abstracts and Google Scholar. Additional grey literature will be sought by searching ETHOS (British Library Electronic Thesis Online), ProQuest Dissertations and Theses, OpenGrey (System for Information on Grey Literature in Europe), the King's Fund Library Database, NHS Evidence and the websites of relevant charities/user groups/professional bodies. Established links with professional networks and relevant NHS organisations will be drawn on to identify further grey literature including unpublished service evaluations.

We will subsequently use 'cluster searching' techniques to identify additional papers that might add to the conceptual richness and contextual thickness including 'sibling' (i.e. directly linked outputs from a single study) and 'kinship' (i.e. associated papers with a shared contextual or conceptual pedigree) papers (17). We will also conduct forward and backward citation searches, using Google Scholar and Web of Science, to identify further related papers from the wider literature, and approach the LEG and SG for recommendations on potentially relevant documents or additional sources to search.

Searching will continue until sufficient data is found ('theoretical saturation') to conclude that the refined programme theory is sufficiently coherent and plausible (16). If the volume of the literature retrieved proves unmanageable, we will employ a variety of appropriate sampling strategies (e.g. theoretical sampling, maximum variation sampling) to ensure that we have sufficient focussed but relevant data for programme theory development (22).

3. Selection, appraisal and data extraction

Documents identified will be screened against inclusion and exclusion criteria:

Inclusion (for literature review)
People living with SMI (schizophrenia, schizoaffective disorder, bipolar disorder and all other non-organic psychoses)
Taking or experience of taking antipsychotics (British National Formulary [BNF] 18, Chapter 4; section 3.6).
Informal (family) carers for people with SMI taking or experience of taking antipsychotics
Practitioners supporting people with SMI taking or experience of taking antipsychotics

Exclusion (for literature review)
People without SMI
Medication other than antipsychotics
Children < 18 years old

Selection and appraisal is a two-step process:

1. Potentially relevant documents will initially be screened by title, abstract and keywords by a member of the research team. A 10% random sample will be checked by CD (any disagreements on the boundaries will be resolved with the input of GW);

2. The full texts of this set of documents will be obtained and screened by a member of the research team. They will read the full text of all the documents that have been included after screening based on title and abstract. Documents will be selected for inclusion when they contain data that is relevant to the realist analysis i.e. could inform some aspect of the programme theory.

Full texts of the included papers will be uploaded onto NVivo. Relevant sections of texts, which have been interpreted as relating to contexts, mechanisms and their relationships to outcomes, will be coded in NVivo. This coding will be inductive (codes created to categorise data reported in included studies), deductive (codes created in advance of data extraction and analysis as informed by the initial programme theory) and retroductive (codes created based on an interpretation of data to infer what the hidden causal forces might be for outcomes). Each new element of data will be used to refine the theory if appropriate, and as the theory is refined, included studies will be re-scrutinised to search for data relevant to the revised theory that may have been missed initially.

The characteristics of the documents will be extracted separately into an Excel spreadsheet, including bibliographic information and details about study design, population and setting.

4. Primary Data Collection

Realist interviews will be conducted to gather additional data to support, refute or refine the programme theory developed from the literature review stream (11). Realist interviews with service users, informal carers, and practitioners will explore our understanding of the CMOCs and programme theory (11). Realist interviews are a sub-type of qualitative interview where the researcher does a 'show and tell' with the participant (23). The participant is eased in and then questioned in the most neutral way possible about aspects of the programme theory.

Method: Interviews and/or focus groups with service users, practitioners and informal carers will be recorded and transcribed verbatim using professional transcribers.

a. Interviews with people with SMI: the interviews will allow targeted exploration of the programme theory with participants with lived experience.

Participants will be purposively sampled to ensure diversity in potentially conceptually-relevant characteristics including, for example, ethnicity, gender, diagnosis and age.

b. Interviews with practitioners (including CPNs [Community Psychiatric Nurses], psychiatrists, GPs, pharmacists, pharmacy technicians, recovery workers, social workers and occupational therapists) who support people with mental health problems. Participants will be purposively sampled to ensure diversity in potentially conceptually relevant characteristics including, for example, locality (rural vs. urban), and the index of deprivation in the area that they work. To aid appropriate identification at NHS Trust level, a member of the research team will regularly update the Trust staff as to which characteristics are still required. E.g., pharmacy technicians may be under represented in the sample or people from ethnic minorities may be under represented.

c. Informal carers will be identified via third sector organisations and/or via service users. Informal carers will either be interviewed with the service user (as part of the dyad), or alone if not recruited as part of a dyad.

Provisionally the interviews and focus groups will explore our programme theory and then enable us to refine our programme theory. Within a realist interview, participants are asked to provide their interpretations and perceptions of the programme theory. Questioning starts with an unfocussed discussion about the programme theory and then gradually 'drills' down into different sections of the programme theory.

Data Analysis: NVivo software will be used to organise and understand the qualitative data. Data analysis will take place after each interview and a use realist logic of analysis. The coding process will be similar to that outlined with the secondary data and be inductive, deductive and retroductive.

All interviews will be recorded and transcribed. For quality control, one member of the team will initially conduct data analysis and coding; a second member of the team will code 10% of interviews to check for consistency in coding with a third resolving any disagreements.

The project management team will regularly meet up to discuss the analysis of the interviews; findings will also be presented to the LEG and SG. Through discussion and disputation with members of both groups and the project management team inferences will be made about how the programme theory should be further refined.

5. Data Analysis, Synthesis and Dissemination

Data analysis will use a realist logic of analysis to make sense of the initial programme theory. Data for analysis will be drawn from following sources: i) documents that have been included in the realist review after screening against inclusion and exclusion criteria and; ii) transcripts of the primary data collected from the interviews and focus groups. As part of our process of analysis a series of questions about the relevance and rigour of content within data sources will be asked (24):

- Relevance: Are sections of text within this document or transcript relevant to programme theory development?

- Rigour (judgements about trustworthiness): Are these data sufficiently trustworthy to warrant making changes to the programme theory?

- Interpretation of meaning: if relevant and trustworthy, do its contents provide data that may be interpreted as functioning as context, mechanism or outcome?

- Interpretations and judgements about Context, Mechanism and Outcome configurations (CMOCs). For example, what is the CMOC (partial or complete) for the data that has been interpreted as functioning as context, mechanism or outcome?

- Interpretations and judgements about programme theory. For example, how does this particular (full or partial) CMOC relate to the programme theory? Within this same document or transcript, are there data, which informs how the CMOC relates to the programme theory?

Data to inform our interpretation of the relationships between contexts, mechanisms and outcomes will be sought across documents and transcripts. Interpretive cross-case comparison will be used to understand and explain how and why observed outcomes have occurred, for example, by comparing settings where interventions to limit antipsychotic weight gain have been reported as being ‘successful’ against those which have not; from this we will understand how context has influenced the results. When working through the questions set out above, where appropriate we will use the following forms of reasoning to make sense of the data: juxtaposition of data, reconciling of data, adjudication of data, and consolidation of data.

Ultimately, our analyses will be used to identify which practical intervention strategies we might be able to use to change existing contexts in such a way that ‘key’ mechanisms are triggered to produce desired outcomes. From this, guidance will be developed for service users and clinicians.

If required, we will identify a sub-group of initial interviewees for a follow-up interview for their opinion on the initial findings and draft guidance. We would aim to re-interview a broadly representative group.

Members of the LEG and SG members will provide feedback on the veracity of the refined CMOCs, the proposed intervention strategies and guidance including the most appropriate format and

dissemination strategies. They will also advise us on the 'real world' feasibility of these strategies. Following this feedback, the guidance will be appropriately modified. We will work with key stakeholder organisations to support the dissemination of our findings and put outputs into practice.

6 STUDY SETTING

The interviews will be conducted in a convenient location for participants, or if required for example due to COVID restrictions, using video-conferencing e.g. MS Teams.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

7.1.1 Service Users

7.1.1.1 Inclusion criteria

People living with SMI (schizophrenia, schizoaffective disorder, bipolar disorder and all other non-organic psychoses)
Currently taking or have previously taken antipsychotics (British National Formulary [BNF] 18, Chapter 4; section 3.6).
Experience of weight gain associated with antipsychotics or related issues
Aged 18 plus

7.1.1.2 Exclusion criteria

Lacks capacity to consent
People without SMI
Children < 18 years old

7.1.2 Informal (Family) Carers

7.1.2.1 Inclusion

Supporting people with SMI currently taking or previously taken antipsychotics who have experienced weight gain associated with antipsychotics or related issues.
Main family carer.

7.1.2.2 Exclusion

Lacks capacity to consent
Children < 18 years old
No experience of supporting people with SMI currently taking or previously taken antipsychotics who have experienced weight gain associated with antipsychotics or related issues.

7.1.3 Clinicians/Practitioners

7.1.3.1 Inclusion

Supporting people with SMI currently taking or previously taken antipsychotics who have experienced weight gain associated with antipsychotics or related issues.

7.1.3.2 Exclusion

No experience of supporting people with SMI currently taking or previously taken antipsychotics who have experienced weight gain associated with antipsychotics or related issues.

7.2 SAMPLING

7.2.1 Size of sample

Sample size: the predicted sample size is up to 30 service users and informal carers, and 20 practitioners, or until data saturation is reached. However, the HRA application will state up to 35 service users and informal carers, and 25 clinicians in case data saturation is not reached at the lower number and to avoid submitting a minor amendment for a small increase in the number of participants interviewed. The sampling strategy will be informed by the literature review and will be directed by the need to find data relevant to explore and refine the programme theory.

7.2.2 Sampling technique

A mixture of convenience, snowball and purposive sampling will be used to identify participants. We will identify participants from a convenient sample pool and purposively sample against certain characteristics (e.g. ethnicity) to achieve a diverse sample. We will then use snowballing from the initial purposive and convenient samples. The PIS will highlight that not everyone who expresses an interest will necessarily be recruited.

7.3 RECRUITMENT

7.3.1 Participant identification

Potential participants will be invited to contact the Research Associate for more information about RESOLVE. The Research Associate will confirm eligibility. All potential participants (service users, family carers, clinicians) will be offered gift vouchers up to a value of £30 as a token of thanks for participation per interview. Specific recruitment strategies to identify potential participants include:

1. Service users and family carers will be recruited via the charitable sector for example the McPin Foundation. Brief information about the study will be disseminated via newsletters, social media etc.

2. The poster will be displayed in suitable locations for example community pharmacies, community mental health teams etc.

3. We will also use our professional links to identify practitioners. Members of the Project Management Team will assist the process. Building on established links we will send brief information about the study to members of the following practitioner organisations that we have established links with e.g., College of Mental Health Pharmacy (CMHP), Society for Academic Primary Care.

4. We will use social media for example Twitter® to raise awareness about the study for example by tweeting links to the poster.

Potentially interested participants identified by (1), (2), (3) or (4) will be invited to contact the Research Associate (RA) or CI for more information (see section 7.3.2 Consent).

NHS Trust will be given the option of being a PIC or a research site.

5. PIC sites will identify participants and obtain consent to contact information. They will provide participants with a participant information leaflet. Contact details will be passed on to the research team at Aston. A member of the research team will follow up with the individuals, obtain consent to participate in an interview and arrange a mutually convenient time for it to take place. Any queries regarding the study will be answered by a member of the research team.

6. Research sites will identify and consent participants. They will provide participant information leaflets, take consent and answer basic queries about the study. Any complex queries can be resolved by the research team at Aston. Consent forms will be forwarded to the research team. If necessary, the research sites can facilitate an introduction to the RA conducting the interview and a mutually convenient time can be found to arrange an interview.

Follow-up interview
At the time of the initial interview participants will be asked if in principle they would be willing to be contacted about a follow-up interview. If they indicated that they are willing, a member of the research team will contact to check whether or not they are still willing to be re-interviewed.

7.3.2 Consent

Informed consent will be ensured by providing written information and where necessary verbal explanations to potential participants and taking recorded written consent using standard consent forms approved by the HRA. Only participants with the capacity to consent to the research will be included in the study. The requirements of the Mental Capacity Act will be fully complied with regarding inclusion of participants who may lack or lose capacity. The same approach for assessing capacity will be used for face-to-face and online/telephone interviews.

For PICs, consent will be taken by one of the Research Associates (RA) in the research team, who has received full NIHR training in GCP, which includes assessing capacity. The RA will obtain support and supervision from the CI, who is a specialist mental health pharmacist with over 20 years' practical clinical experience of working with individuals with mental illness, and experience of research in participants who may lack capacity. In addition, the CI has also undertaken NIHR training in GCP, which includes assessing capacity.

Those interested in taking part will be able to express an interest in the study by contacting the research tem directly. Eligibility will be checked during an initial telephone call with one of the research team. All potentially eligible participants will receive clear information about the nature and objectives of the study and possible risks associated with their participation and be given an opportunity to ask questions. Potential participants will also be supplied with written material (e.g., information leaflet and consent documents) approved by the REC. Interviews will be face-to-face or online/telephone depending upon the preference of the participant. Written consent, including assessing capacity will be taken at the point of participation using standard consent forms.

For research sites, eligibility and consent to participate will be taken by the research staff at the relevant NHS Trust and we will ensure that they have undertaken GCP training and taking informed consent from adults lacking capacity. All potentially eligible participants will receive clear information about the nature and objectives of the study (e.g., information leaflet and consent documents) and possible risks associated with their participation, and be given an opportunity to ask questions, either to the staff within the NHS Trust or to the research team directly. Research staff at the NHS Trust will forward completed consent forms and contact information to the research team to arrange an interview. Where necessary, NHS staff can facilitate introductions to the research team and interviews can be arranged at this point. Interviews will be face-to-face or online/telephone depending upon the preference of the participant. Written consent, including assessing capacity will be taken at the point of participation using standard consent forms. Eligibility and consent will be confirmed by one of the research team at the beginning of the interview.

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Assessment and management of risk

The risks associated with this non-interventional study are low. However, there is the potential for participants to become upset when discussing sensitive topics (e.g. illness, personal wellbeing, medication). Prior to the interview, the researcher will make it clear to participants that they have the right not to answer questions that they do not wish to, pause the interview at any point and resume at a later date, or withdraw from the study altogether at any point during the interview. If a participant is showing signs of distress during the interview, the researcher will stop the interview in the best interests of the participant, immediate support will be provided and details of additional possible support supplied (e.g. care coordinator, appropriate mental health helpline).

Participants may feel that their participation will have an impact upon their care or work life (in the case of care professionals). In order to address this issue, all participants will be fully briefed about the study procedures in place to maintain confidentiality prior to taking part in the study. There is also a possibility that a participant may raise a concern about the well-being of a participant or a safeguarding issue. If this occurs, the issue will be discussed with the person making the disclosure and then if appropriate the RA will discuss the issue with the CI and report the matter to the relevant bodies (e.g. CQC, GPhC). Ensuring the safety, well-being and confidence of participants in the research is the prime concern throughout.

All members of the research team will receive appropriate training, as required, prior to undertaking the interviews, and ongoing support and supervision from IM and other members of the team throughout the project. The safety of the research team will be protected by adhering to Aston University's Lone Working Guidance. The NIHR Safeguarding policy will be followed at all times.

8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from a REC for the study protocol, informed consent forms and other relevant documents e.g. advertisements.

Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.

All REC correspondence will be retained.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.

If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

Regulatory Review & Compliance

The Chief Investigator or designee will ensure that appropriate approvals from participating organisations are in place. The sponsor will ensure that all required approvals are obtained from participating organisations.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the

study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

Amendments

If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

Amendments also need to be notified to the national coordinating function of the UK country where the lead NHS R&D office is based and communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site. Note that some amendments that may be considered to be non-substantial for the purposes of REC still need to be notified to NHS R&D (e.g. a change to the funding arrangements).

The chief investigator will have overall responsibility for making amendments and in discussion with the sponsor deciding whether the amendment is substantial or non-substantial. Substantive changes will be communicated to relevant stakeholders via the usual procedures and the protocol tracked to identify the most recent protocol version.

8.3 Peer review

The study protocol has received proportionate review by the funders and their independent expert delegates as part of the standard funding process.

8.4 Patient & Public Involvement

PPI with be provided by an ongoing Lived Experience Group (LEG). Members will represent a diverse range of people, in terms of ethnicity, gender and age, to promote inclusion, diversity and equality in our approach. The McPin Foundation will coordinate PPI, which will be conducted in line with UK Standards for Public Involvement, as a minimum. All those involved in the LEG will be paid for their time.

PPI is embedded throughout RESOLVE, and service users have and will advise on:

a. Theory development: advice on developing the initial programme theory and the relevance and interpretation of the literature.

b. Management: recruitment, consent, and participant information including the acceptability of our recruitment and consent methods.

c. Research design: helping to develop research instruments (e.g. interview questions).

d. Analysis: outputs will be presented to service users for their comments on what is likely to be more or less helpful and amended appropriately.

e. Dissemination: PPI representatives will be invited to co-author outputs. We will support a service user to be first author on a paper describing service user input, and present at conferences.

8.5 Protocol compliance

Protocol deviations will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

8.6 Data protection and patient confidentiality

All investigators and study site staff must comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

All digital data will be kept on password protected Aston computers, and printed copies and consent-related documents will be stored in a site file kept in a locked filing cabinet within a secure office at Aston University. Anonymised audio recordings of interviews will be transcribed verbatim by a professional transcription service provider: The Typing Works (who have been used previously by Aston under a standard data Processing Agreement). Data will be transferred to the transcription service providers using secure file transfer.

The identity of participants will be kept confidential by providing a unique participant identifier to each participant when consent is taken and all information that may make the participant identifiable will be removed from the printed transcripts. Any extracts from interview transcripts that are utilised in publications will be used under a pseudonym in order to protect the identity of participants and ensure anonymity. The ways in which confidentiality and anonymity will be managed will be explained to participants.

One of the research team will check the accuracy of recordings by listening to the audio recording of each interview alongside the written transcript and making amendments to the transcript if required. The audio recording will be destroyed once the final report is published. Contact details (e.g. address, email address) of participants who requested a summary will also be destroyed at this stage. Anonymised data will be kept for 6 years after completion of the study to support dissemination and to contribute to the understanding of the issue. It will then be destroyed by the CI.

8.7 Indemnity

Insurance and/or indemnity to meet the potential legal liability of the sponsor for harm to participants arising from the **management** of the research will be covered by Aston University insurance.

Insurance and/or indemnity to meet the potential legal liability of the sponsor or employer for harm to participants arising from the **design** of the research will be covered by Aston University insurance.

Insurance and/or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the **conduct** of the research will be covered by the NHS indemnity scheme or professional indemnity for participants recruited at NHS sites only, and Aston University insurance will apply for research sites that that are not covered by the NHS indemnity scheme.

No equipment will be provided to NHS sites for the purposes of this study.

8.8 Access to the final study dataset

Only members of the Project Management Team will have access to the full anonymised dataset. The dataset will be used for appropriate secondary analysis (due to iterative nature of qualitative research what these analyses will focus on will not be clear until after the data is collected). The consent form will include permission to use the interview data for appropriate analyses within the overall scope of the project.

9 DISSEMINIATION POLICY

9.1 Dissemination policy

On completion of RESOLVE, the data will be analysed and tabulated and a Final Study Report produced for the funders. The report, as will all papers from RESOLVE, be available Open Access online. The funding body will be acknowledged as per standard NIHR criteria.

If desired, participants will be notified about the outcome of the study by provision of the publication, and a specifically designed newsletter. Participants will indicate as part of the consent procedure whether, or not they would like to be notified about the outcome of the study and receive the newsletter.

Due to the qualitative nature of the data it is not possible to make the full dataset (e.g. interview transcripts) publicly available.

9.2 Authorship eligibility guidelines

All co-applicants and any others who make a substantial contribution (as defined by the International Committee of Medical Journal Editors criteria) will be co-authors of the final study report and any other publications.

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11. APPENDICIES

11.1 Appendix 1 - Required documentation

CVs of the research team.

Participant Information Sheet (PIS) on headed paper.

Consent forms on headed paper.

Recruitment poster.

Interview Schedules

12.1 Appendix 2 – Amendment History

Details of all protocol amendments are listed below.

Protocol version no.	Date issued	Details
V0.1	3rd August 2021	Sent to sponsors for comments
V0.2	8th September 2021	Re-drafted in line with sponsor's comments – send to co-applicants for comments.
V1	15th September 2021	Added further details of organisations that we will link with to support recruitment; signatures obtained
V1.1	27th September 2021	Sent to funders: Added further clarification on inclusion/exclusion for realist review (page 3)
V1.2	28th September 2021	Added further clarification on inclusion/exclusion for realist review (page 3)
V1.3	29th March 2022	Methods for re-interviewing (section 5). Added further details on recruitment via the NHS (section 7.3.1).
V 1.4	16th December 2022	Research sites added as a site type New research sites will take consent and facilitate introductions to the RA. Other member of the research team may undertake interviews Minor changes to study documentation to reflect change in title (e.g., from Dr to Professor) and the creation of a study email address. Space added for Trusts to localise information Addition of new researchers to the team Creation of a new form to record demographic information Protocol change to reflect that new members of the team will need to be trained to undertake interviews.