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Bridging the gap between physical and mental illness in community pharmacy (PharMIbridge): protocol for an Australian cluster randomised controlled trial

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2
3 **Title: Bridging the gap between physical and mental illness in community pharmacy**
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5 **(PharMIbridge): protocol for an Australian cluster randomised controlled trial**
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55 physical health, medication adherence
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ABSTRACT

Introduction There is a significant life expectancy gap attributable to physical comorbidities for people living with severe and persistent mental illness (SPMI) compared to the general population. Medications are a major treatment for SPMI management and physical illnesses, hence pharmacists are well-positioned to support mental healthcare and comorbidities. The RCT aim is to evaluate effectiveness of an individualised, pharmacist-led, support service for people experiencing SPMI focusing on medication adherence and physical comorbidity management, compared to standard care (a medication-management service; MedsCheck).

Methods and analysis *PharMIbridge* is a cluster RCT, whereby community pharmacies in four Australian regions will be randomised (1:1 ratio), to either Intervention Group (IG) or Comparator Group (CG). All IG and CG pharmacy staff will receive Blended-Mental Health First Aid training. Additionally, IG pharmacists will receive further training on medication adherence, goal setting, motivational interviewing, managing physical health concerns and complex issues relating to psychotropic medication. CG pharmacists will not receive additional training, and will provide standard care (MedsCheck). The primary outcome will be change in participants medication adherence over 6-months. Using mixed-effects logistic regression model and a cluster size of 48 pharmacies, a total of 190 participants will need to be recruited to each arm to find a statistically significant difference in medication adherence. Secondary outcomes will be changes in factors associated with cardiometabolic risk and quality of life, emphasising physical and psychological wellbeing; medication-related problems; pharmacists knowledge, confidence and ability to support people experiencing SPMI; and effects on healthcare utilisation. A within RCT-based economic evaluation comparing the intervention with standard care will be undertaken.

Ethics and dissemination The protocol and pharmacist training program received Griffith University Human Research Ethics Committee approval (HREC/2019/473 and

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3 HREC/2019/493 respectively). Results will be published in peer-reviewed journals and
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5 available at Sixth Community Pharmacy Agreement website (<http://6cpa.com.au/about-6cpa/>).
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8 **Trial Registration Number:** ANZCTR;processing
9

10 **Strengths and limitations of this study**

- 13 • The *PharMIbridge* RCT builds on previous Australian research to test the effectiveness
14 of a pharmacist-led medication support service for consumers living with SPMI, with
15 an additional focus on the management of physical comorbidities which are highly
16 prevalent in this population.
17
- 18 • A multi-disciplinary approach will encourage participating pharmacies to develop and
19 maintain working relationships with local GP clinics, medical centres, mental health
20 care teams, and other physical health/exercise centres and practitioners (e.g. gyms)
21 beyond the life of the RCT.
22
- 23 • Routinely collected pharmacy dispensing and Pharmaceutical Benefits Scheme (PBS)
24 data will be used, alongside self-reported measurements, to evaluate medication
25 adherence, which is the primary outcome measure.
26
- 27 • While a key focus of this RCT is exploring the impact of the *PharMIbridge* intervention
28 on the physical wellbeing and overall health of people living with SPMI, the follow-up
29 time is insufficient to use these and related outcomes as primary outcome measures.
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- 31 • It is not possible for pharmacy staff or consumer participants to be blind to service
32 allocation, due to the nature of the intervention.
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51 **BACKGROUND AND RATIONALE**

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54 Community pharmacists are highly trusted and essential members of the primary healthcare
55 team, playing a vital role through medication supply and information provision. Given the
56
57 accessibility of community pharmacies, pharmacists are in an ideal position to adopt a triage-
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3 style role, signposting to other health care professionals and services. There is an emerging
4
5 role, and growing need, for community pharmacists to support and manage mental illnesses.
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7 Research has demonstrated that pharmacists are capable of identifying consumers at risk of
8
9 depression and referring appropriately for diagnosis and therapy,¹⁻³ managing psychotropic
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11 (e.g. antipsychotic and mood stabiliser) medication-related problems (MRPs),⁴⁻⁷ providing
12
13 antidepressant adherence support, and working within multidisciplinary mental health care
14
15 teams.⁸⁻¹⁰
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19 However, evidence also suggests that health care professionals, including pharmacists,
20
21 are not exempt from holding stigmatising attitudes and behaviours towards mental health
22
23 consumers;^{11 12} pharmacists with more marked stigmatising attitudes were reported to be less
24
25 willing to provide professional services to people with severe and persistent mental illness
26
27 (SPMI)*.¹⁴ Lack of training in mental health or the opportunity to acquire the necessary skills
28
29 and confidence in working with mental health consumers, have been cited as barriers to
30
31 providing appropriate and timely care for this population.¹⁵ Hence, the urgent need to develop
32
33 a training program that addresses pharmacists' mental health knowledge gaps in anticipation
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35 of improving attitudes towards, and confidence in, providing care for people living with SPMI.
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37 This is particularly important in the Australian context given that 61.5% of people who
38
39 experience psychosis, do so on multiple occasions, with partial or complete remission of
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41 symptoms between episodes.¹⁶ Also of relevance is that a substantial proportion of Australians
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43 using psychotropic medications access health care services in community settings, with 39-
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45 million mental health-related prescriptions dispensed in Australia in 2018-19.¹⁷
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51 Of significant concern is that Australians living with SPMI also experience poor physical
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53 health; they are five times more likely to smoke, six times more likely to die from
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55 cardiovascular disease and four times more likely to die from respiratory disease than the
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3 general population, leading to a 14-23 year gap in life expectancy.¹⁸ These issues are often
4 overlooked and/or dismissed by health care professionals and policy makers.¹⁹ For example, a
5 study by Morant et al.²⁰ in the United Kingdom found that the physical health concerns of
6 antipsychotic users were not addressed by prescribing psychiatrists. Decisive action is needed
7 to engage both relevant health practitioner groups and people living with SPMI with respect to
8 physical health management.²¹
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17 The acceptability of medications by people living with SPMI is also problematic and
18 adherence is poor.²² Reasons include, but are not limited to, experiencing (or the risk of
19 experiencing) unwanted side effects, reluctance to rely on medication, and forgetfulness.²² Poor
20 adherence with antipsychotics is a key reason for relapse in psychosis; even missing a few days
21 of treatment substantially increases this risk.²³ However, a good therapeutic relationship with
22 attending health practitioners is linked to better medication adherence, fewer hospital
23 admissions and a reduction in self-harm in people experiencing psychosis.²⁴ In this respect,
24 pharmacist-led medication reviews for mental health consumers have shown promising
25 results,^{7 25} and given the associated concerns with drug-drug interactions, are particularly
26 relevant for those living with SPMI using psychotropic medications.
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42 **Evidence gap**

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44 Overall, there is relatively limited research on improving outcomes for consumers living with
45 SPMI in the primary care setting (including community pharmacy). Whilst research exploring
46 the impact of medication reviews on psychotropic prescribing within residential aged care
47 settings has been conducted,²⁶ few studies have involved participants using psychotropic
48 medications living in the community,^{27 28} particularly those experiencing SPMI.²⁹ While
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3 Australian pharmacists can provide a medication review service in the form of a MedsCheck[†]
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5 within the community pharmacy setting, research exploring the impact of this service on
6
7 medication adherence is limited.³⁰⁻³³
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10 To our knowledge, research exploring the impact of a community pharmacist-delivered
11 medication or health-related service specifically for people living with SPMI is scarce A
12
13 Canadian study demonstrated that pharmacy staff supported mental health consumers by
14 providing follow-up care which focused on medication management and improving health
15 service navigation and most study participants were using multiple psychotropic medications,
16
17 few were living with SPMI (n=36; 17.9%).^{34 35} Additionally, results from an Australian
18
19 community-based, pharmacist-led medication support service for participants living with
20 depression and anxiety were positive with significant improvements in relation to participants
21 illness perceptions, medication satisfaction and medication adherence.⁶ Our proposed
22
23 Randomised Controlled Trial (RCT) builds and expands on this evidence to test the
24 effectiveness of a person-centred, goal-oriented, and flexible, pharmacist-led support service
25 for people living with SPMI, with a specific focus on improving medication adherence and
26 managing physical comorbidities. For the purpose of this RCT, SPMI refers to any mental
27
28 illness that has a continuous and significant effect on a person's daily life, and includes (but is
29 not limited to) the following: schizophrenia and other psychotic disorders, severe and recurrent
30 depression, and bipolar disorder.
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46 **Study objectives**

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48 The aim of this RCT is to evaluate the effectiveness of “Bridging the Gap between Physical
49 and Mental Illness in Community Pharmacy (*PharMIbridge*)”; an intervention comprising an
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[†]A MedsCheck is an Australian remunerated service which involves a community pharmacist reviewing a person's medication, identifying any medication-related problems (MRPs), and providing related medication information. Australian residents eligible for a MedsCheck service include consumers who are at a higher risk of MRPs, such as those using more than five prescription medicines.³⁰
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3 individualised, pharmacist-led, support service for people living with SPMI, compared to
4 standard care involving a one-off medication management service (MedsCheck). The primary
5 objective is to test the impact of the *PharMIbridge* intervention (Intervention Group; IG) on
6 medication adherence. It is hypothesised that the *PharMIbridge* intervention will demonstrate
7 a 20% increase in adherence at six-months compared with standard care (Comparator Group;
8 CG). Overall, the objectives of the *PharMIbridge* RCT are to assess changes in:
9

- 10 • medication adherence;
- 11 • health outcomes including quality of life, physical health and psychological wellbeing;
- 12 • community pharmacists' confidence, knowledge and ability to address the medication-
13 related and physical health care needs of people living with SPMI; and,
- 14 • health care service acceptability, utilisation and cost-effectiveness

15 The findings will be used to inform a more widespread implementation of person-centred
16 service models for people living with SPMI within the primary healthcare sector.
17

18 **METHODS**

19 Using a cluster RCT design, community pharmacies will be randomised to deliver either:
20

- 21 i) the *PharMIbridge* intervention; or,
- 22 ii) standard care involving a one-off MedsCheck service.

23 Figure 1 provides an overview of the research design, which involves a partnership
24 between two University institutions (Griffith University and The University of Sydney) and
25 two professional pharmacy organisations (The Pharmacy Guild of Australia and The
26 Pharmaceutical Society of Australia). Genuine engagement throughout the entire RCT with
27 individuals with lived experiences of SPMI is critical to success. Given that those living with
28 SPMI require a multifaceted approach to meet their mental and physical health care needs, a
29 multidisciplinary team is also a key component of the *PharMIbridge* RCT. An Expert Panel
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3 will be formed, with invitations extended to consumer representatives living with SPMI, and
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5 representatives from key organisations such as Mental Health Australia, National Mental
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7 Health Consumer and Carer Forum, Sane Australia, the Royal Australian and New Zealand
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9 College of Psychiatrists (RANZCP), and the Royal Australian College of General Practitioners
10
11 (RACGP). The Expert Panel will provide the research team with guidance on the
12
13 implementation of the RCT, including advice on consumer and healthcare professional
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15 engagement, training materials and other resources, and research translation. The research team
16
17 will work with local Primary Health Networks (PHNs)[‡] across RCT sites to recruit eligible
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19 community pharmacies into the *PharMIbridge* RCT.
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[‡] PHNs are independent organisations funded by the Australian Government. They work closely with local hospital networks and each PHN is overseen by a board of medical professionals. PHNs conduct assessments of the health needs of their region to identify groups of people who need more resources, programs and services. The information helps PHNs to tailor health services to meet the community's needs (<https://www.healthdirect.gov.au/primary-health-networks-phns>). 8

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Insert Figure 1 about here

Study setting and population

This RCT will be conducted in four Australian regions including urban, rural and remote. Two regions in Western Australia (WA) (i.e. South-West and Metropolitan/South Perth), one region in New South Wales (NSW) (i.e. Hunter New England) and the Australian Capital Territory (ACT) will be included. RCT sites will include a mix of community pharmacies within varied PhARIA (Pharmacy Accessibility/Remoteness Index of Australia classification) locations,³⁶ while also ensuring pharmacies ability to meet the eligibility criteria and recruit the required number of consumer participants. For example, the South-West region of WA includes a mix of regional and remote areas and has a high need for mental health services, with only 6% of the affected population reported to be receiving appropriate care for their mental health problems.³⁷

Community pharmacies

Community pharmacies located within the selected RCT regions will be eligible if they have:

- i) approval to dispense pharmaceutical benefits as part of the Pharmaceutical Benefits Scheme (PBS);
- ii) accreditation for Quality Care Pharmacy standards (quality assurance program for community pharmacies);
- iii) a clientele demographic that includes people with SPMI;
- iv) routinely provided MedsCheck as an established professional service;
- v) guaranteed that the *PharMIbridge* intervention will be carried out by a registered pharmacist who has completed the training;
- vi) a private room/area for confidential conversations and assessments;
- vii) pharmacy owner/manager consent to participate; and,

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3 viii) an established working relationship with local GP clinics or centres, mental health
4 care teams, and/or are already engaged with mental health promotion.
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8 Pharmacies will be randomised into the IG or CG after stratification by region and
9
10 geographic location (urban/rural/remote). Within each stratum, pharmacies will be randomly
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12 allocated in a ratio of 1:1 to the IG or CG. Randomisation will occur after all pharmacies for
13
14 that RCT region have been recruited. The number of full-time equivalent employees will be
15
16 ranked within each stratum, and pharmacies will be formed into pairs. A list of computer-
17
18 generated random numbers will be used to allocate either the PharMIbridge intervention (IG)
19
20 or MedsCheck service (CG) to the first of each pair; the second in each pair will be allocated
21
22 the alternative service. It is expected that 12 pharmacies will be located in urban, nine in
23
24 regional/rural and three in remote areas in each of the RCT arms.
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30 31 Consumer participants

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33 Trained pharmacy staff (CG and IG) will identify ten eligible consumers per pharmacy for an
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35 enrolment period of six months. Consumers can also self-identify into the RCT via research
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37 promotion or be referred directly from a treating health care professional, non-government
38
39 organisation or mental health service. Eligible consumers need to have capacity to provide
40
41 informed consent, as assessed by trained pharmacy staff using capacity assessment principles
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43 for RCT participation, and consent to pharmacists contacting their treating healthcare team
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45 (e.g. GP, case manager, psychiatrist).³⁸ Furthermore, eligible consumers need to provide
46
47 consent to allow the researchers to access their associated Medicare Benefits Schedule (MBS),
48
49 PBS, hospitalisation and emergency department records for a 12-month pre- and 6-month post-
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51 trial period. Specifically, eligibility will require participants to:
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- 54 i) be 16 years and over and residing in the community;
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3 ii) be using at least one antipsychotic or mood stabiliser for at least six-months
4 continuously, for the treatment of SPMI; and,
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8 iii) have a complex medication need (e.g. adherence concerns) or unmanaged physical
9 health problems.
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12 Although participants need 6-months of dispensing data for a psychotropic medicine
13 prior to RCT enrolment, medication changes during this time are reasonable, as well as the use
14 of other medication(s) for their mental and physical health. Exclusion criteria include:
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19 i) aged under 16 years;
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21 ii) unstable mental health symptoms or deemed as an unsuitable RCT participant by
22 their treating health care professionals, pharmacist or carer;
23
24 iii) 'when required' or inconsistent use of antipsychotic and/or mood stabiliser
25 medication(s);
26
27 iv) using an antipsychotic or mood stabiliser medication for treatment of an illness not
28 related to SPMI (e.g. off-label use of quetiapine for sleep or anxiety);
29
30 v) not consenting to participate to the researchers contacting their treating healthcare
31 practitioner, or to accessing PBS, MBS and hospitalisation data; and,
32
33 vi) receiving a MedsCheck or Home Medicines Review (HMR)[§] within 12-months
34 prior to RCT enrolment.
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***PharMIbridge* intervention**

An overview of the proposed *PharMIbridge* RCT is illustrated in Figure 2. The intervention will be undertaken by trained community pharmacists randomised into the IG. In addition to the standard care available in all community pharmacies, the intervention will provide IG consumer participants with an in-depth service that is goal-oriented, flexible and individualised. Goals will be guided by an in-depth medication review, various self-assessment questionnaires and tools (documented during the Initial Health Review consultation) and be tailored to meet individual needs. There will be a specific focus on overcoming barriers to medication adherence and addressing physical health concerns (Table 1). RCT questionnaires and tools are reported under *Study outcomes*.

Insert Figure 2 about here

IG consumer participants will receive individualised care and support over a six month period (Figure 2) to promote medication adherence, optimise the management of their mental illness, and encourage lifestyle and pharmacological strategies to improve physical health, with a particular focus on reducing cardiometabolic risk. During the initial consultation (Figure 2), IG pharmacists will utilise motivational interviewing techniques to determine participants' key concerns regarding their medication, adherence, and physical and psychological wellbeing. Upon identification of three to five key issues, IG pharmacists will: i) engage participants in a goal-setting discussion and explore strategies to achieve these goals; ii) complete a signed agreement of the support plan; and iii) confirm participant's consent to discuss this plan with their nominated healthcare professional (e.g. GP, psychiatrist, case manager, etc.). The pharmacist will continue to work with the participant over the 6-month intervention period towards goal achievement, with follow-ups as identified with the participant and in their preferred modality (face-to-face, email, telephone, text messaging). At a minimum, it is expected that participants will have at least three face-to-face consultations with IG pharmacists (including the Initial and Final Health Review consultations). However, additional

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3 consultations can occur during the RCT period and participants can obtain pharmacist advice at any
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5 time, as needed. At the final 6-month follow-up the IG pharmacist and participant will complete the
6
7 Final Health Review.
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10 IG pharmacists will be required to keep accurate records of interactions and outcomes using a
11
12 cloud-based software platform (GuildCare NG™), which is currently used in many community
13
14 pharmacies when delivering professional services. Support plans, medication-related reports and
15
16 follow-up consultations, recorded as part of the *PharMIbridge* intervention, will be accessible to a
17
18 participant's nominated health care professional for their direct input, through GuildCare NG™. IG
19
20 pharmacists will work collaboratively with participants' nominated healthcare practitioner(s),
21
22 updating them regularly via the Guildcare platform and usual communication mechanisms
23
24 especially when there are any concerns needing rapid intervention.
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35 **Comparator arm**

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37 Participants recruited by a CG pharmacy will receive a standard MedsCheck service after enrolment
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39 and then continue to receive the usual care that the community pharmacy provides. All requirements
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41 outlined for the MedsCheck service will be followed, noting that some participants may not have
42
43 otherwise been eligible for this government funded service (e.g. not taking five or more medicines).
44
45 Pharmacists will schedule a follow-up consultation to complete final RCT outcome assessments
46
47 with participants six-months following recruitment into the RCT.
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53 **Training**

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55 Previous evidence-based programs will inform the development of the education and training
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57 materials for the RCT. This includes the training modules used in the Australian mental health
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3 feasibility study,³⁹ as well as research into pharmacists' knowledge and mental health literacy,⁴⁰
4 mental health stigma,^{14 41} Mental Health First Aid[#] (MHFA),⁴² simulated patient assessments,^{43 44}
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6 consumer-led education,⁴⁵ consumer perspectives and consumer/carer trainers.⁴⁶⁻⁴⁸ A training
7
8 working group will oversee and develop the training content required to deliver the intervention.
9
10 This group will comprise representation from content experts, consumer representatives and the
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12 partner organisations. Face and content validity of all newly developed training material will be
13
14 ensured through collaborations with mental health consumers, the multidisciplinary Expert Panel
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16 and professional pharmacy and mental health organisations. Training will be delivered in such a
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18 way that it facilitates a naturalistic approach to enable pharmacists to use their discretion to
19
20 individually tailor the *PharMIbridge* intervention for each participant.
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26 Training will involve a one or two-day program depending on RCT arm allocation, with IG
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28 pharmacists attending both training days:
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- 30 • First training day

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32 Pharmacy staff in both IG and CG arms will complete Blended MHFA for Pharmacy (B-MHFAP)[≠]
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34 training, involving a six-hour online module completed prior to attending the half-day face-to-face
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36 training component.⁴⁹ It will be delivered by an accredited instructor and is certified for 24
37
38 Continuing Professional Development points. Training on research processes, including participant
39
40 recruitment and consent, service delivery, and use of GuildCare NGTM as a platform for all data
41
42 collection, will be delivered to both IG and CG pharmacy staff in separate groups to ensure they are
43
44 'research-ready.' Established guidelines for providing MedsCheck services will be utilised by CG
45
46 pharmacists.⁵¹ A standard operating procedure (SOP) will be provided to all pharmacists outlining
47
48 the various steps in the research process.
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60 [≠] The blended MHFA in the Pharmacy (B-MHFAP) course uses case-studies, videos and resources tailored to pharmacy staff learning needs and is completed in a blended format, combining eLearning and a follow-up 4-hour face-to-face session.
<https://mhfa.com.au/courses/public/types/blendedpharmacy>

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3 The remainder of the first day of training for IG pharmacy staff will involve the use of
4 simulated patient role-plays with the accredited B-MHFAP instructors and mental health consumers
5 to encourage staff to practice their newly acquired MHFA skills.^{43 44 50} Simulated patient role-plays
6 with on-the-spot performance feedback will allow pharmacy staff to demonstrate their newly
7 acquired skills in a safe, authentic and supportive learning environment. Research has highlighted
8 the importance of behavioural assessments post-training due to the potential for over, and/or under,
9 estimating skills through self-reported measures.⁴³ Research has also indicated that both participants
10 and observers of simulated B-MHFAP role-plays report higher self-reported confidence than those
11 who receive MHFA only, and that maintain improvements in confidence post-training.⁴⁴

- Second training day

12 IG pharmacists will be required to complete four interactive training modules on key issues
13 associated with psychotropic medication use and physical health, and how to address these issues
14 for people living with SPMI, using evidence-based tools. The modules will be developed by the
15 training working group and led by experts (including psychiatrists, psychopharmacologists, and
16 consumer consultants) and will include the following topics:

1. *Complex issues relating to psychotropic medication (adherence and side effects)*. This module will discuss the role of psychotropic medications, including an exploration of the barriers and enablers to adherence, and the consequences of poor adherence. It will also discuss complex issues relating to psychotropic medication use, such as weight gain and diabetes.
2. *Physical health issues for people living with SPMI*. This module will explore the evidence regarding the importance of physical health care and exercise for people living with SPMI. It will also include information on active lifestyles, cardiometabolic risk, tobacco use and resources.
3. *Evidence-based strategies to improve medication adherence and physical health care*. This module will equip pharmacists with evidence-based strategies including guidance on

1
2
3 addressing cardiovascular risk factors, and sensitive issues such as weight management,
4
5 smoking cessation, dental health, and medication adherence.
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- 8 4. *Communication, motivational interviewing and goal setting.* This module will help pharmacists
9
10 develop appropriate and person-centred communication skills and strategies to work with
11
12 participants to set, and reach, their mental and physical health goals.
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14
15 Case studies and role-play activities will be integrated throughout the modules to provide IG
16
17 pharmacists with opportunities to practice and apply their newly acquired skills, including the use
18
19 of research tools and questionnaires. Prior to the first workshop commencing specific aspects of the
20
21 training will be video-recorded to consistency in delivering the intervention to all workshops. The
22
23 training modules will be made available online for IG pharmacists to access as needed for reference
24
25 purposes.
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28
29 The continued wellbeing of participants living with SPMI is a key aspect of the training.
30
31 Information on mental health and crisis support numbers and websites will be part of the resources
32
33 provided, e.g. Lifeline, BeyondBlue. Furthermore, communication between pharmacists and the
34
35 participant's treating team will be ongoing throughout the RCT, thus helping to ensure that any
36
37 deterioration in health status, or concerns about wellbeing, will be immediately recognised and
38
39 addressed.
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45 Recruited community pharmacies will be required to send at least two pharmacists (one of
46
47 whom can be an intern pharmacist^Ø working under the supervision of a registered pharmacist) to
48
49 complete the *PharMIbridge* training components. All pharmacies will be encouraged to invite
50
51 additional pharmacy support staff to complete and attend the B-MHFAP component and
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53 information session on research processes, to support pharmacists in delivering the intervention/
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55 comparator and establish 'Mental Health Friendly Pharmacies'. Ultimately, trained registered
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3 pharmacists will take responsibility for delivering the *PharMIbridge* intervention. For example,
4 while only the pharmacist can be involved in addressing MRPs, a pharmacy support staff member
5 with well-established consumer relationships could assist with promotion, be involved with
6 identifying eligible participants, making follow-up appointments, or sending reminders.
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12 A pilot workshop of the non-B-MHFAP training components will involve a convenience
13 sample of pharmacy students, intern and registered pharmacists, and all RCT trainers/mentors.
14 Feedback will be sought through pre- and post-training questionnaires and focus group discussions
15 at the conclusion of pilot training. This feedback will help identify whether modifications to the
16 training are required prior to its delivery as part of the RCT.
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26 Training mentors

27 The IG training components will be delivered by a local pharmacist and consumer mentor
28 partnership in each RCT region who will also provide ongoing support for IG pharmacy staff
29 throughout the RCT. The combination of a pharmacist educator with experience in community
30 pharmacy practice and a consumer educator with lived experience of mental illness working as a
31 mentor pair has been shown to facilitate implementation of a mental health support service for
32 consumers with depression and anxiety.⁴⁶ The mentor pair will personally visit the IG pharmacies
33 in their RCT region on a minimum of two occasions during the intervention period. In addition to
34 these visits, mentors will provide regular support through phone calls, emails and other modalities,
35 as required. Moreover, the training team will provide two refresher webinars in each RCT region;
36 these will be led by the two mentors. Webinars will focus on problem-solving discussions and co-
37 learning perhaps using examples of ‘what has worked well’/‘not so well’ to stimulate conversation.
38 Refresher content will be based on two additional, pre-recorded, case-scenarios allowing
39 pharmacists to revise the skills they have been applying in practice.
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Study outcomes

Primary outcome

The primary outcome is the difference in medication adherence rates between the IG and CG at RCT conclusion (six-months). Medication adherence will be identified using both routinely collected data (pharmacy dispensing and PBS) and self-reported measurements of adherence; the Reported Adherence to Medicine (RAM)⁵² scale which has been validated for use among people with psychosis, schizoaffective disorder and schizophrenia.⁵³ PBS and pharmacy dispensing data will be used to confirm self-reported data by calculating: i) the Medicine Possession Ratio (MPR), which refers to the proportion of days that a consumer is in possession of their medicine within a defined period; and ii) Medicine Persistence, which refers to a specified time-period when there has been a delay in medicine re-fill.⁵⁴ A pilot of the selected tools will be undertaken in the set-up stage of the *PharMIbridge* RCT (Figure 1 and Table 1) to ensure that they are practical, valid and feasible to use within the RCT time-frame.

Secondary outcomes

Health outcomes

Clinical measures including weight, body mass index, abdominal girth and blood pressure,⁵⁵ will be collected at two time-points; when participants complete the baseline and 6-month follow-up questionnaires. Pharmacists will collect these measures in the pharmacy and/or from patient/health care records. Additionally, participants will be asked (at baseline and 6-month follow-up) if, in the last 12 months, they have had a risk assessment for cardiovascular disease and a glycated haemoglobin (HbA1c) blood test to assess for diabetes. Participants physical health will be evaluated using self-reported questionnaires, including the Physical Activity "Vital Sign" (PAVS) Questionnaire⁵⁶ and selected questions from the Australian Health Survey on Dietary Behaviour.⁵⁷

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3 The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) will also be used to
4
5 screen for substance use.^{58 59}
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8 Additional tools such as the My Medicines and Me Questionnaire (M3Q)⁶⁰ exploring
9
10 psychotropic medication side-effects; the Simple Physical Activity Questionnaire (SIMPAQ)^{61 62}
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12 which identifies time spent on physical activity; the Pittsburgh Sleep Quality Index (PSQI)⁶³
13
14 exploring sleep quality, the Fagerström Test for Nicotine Dependence⁶⁴ and the Brief Pain Inventory
15
16 (BPI)⁶⁶ identifying pain-related concerns, will assist IG pharmacists with intervention delivery.^{65 66}
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18 This combined information will inform the development of goals for IG consumer participants, with
19
20 goal achievement reviewed at each follow-up, and at the final six-month, consultation using the
21
22 Goal Attainment Scale (GAS).⁶⁷
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25 26 *Quality of life, medication experiences and illness beliefs* 27

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29 Difference in self-reported quality of life (e.g. Assessment of Quality of Life, AQoL-6D),⁶⁸
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31 psychological wellbeing (Kessler Psychological Distress Scale, K-6), sleep problems (Insomnia
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33 Severity Index, ISI),⁶⁹ medication burden (Multimorbidity Treatment Burden Questionnaire,
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35 MTBQ),⁷⁰ attitudes (Drug Attitude Inventory 10, DAI-10),^{71 72} illness beliefs (Brief Illness
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37 Perception Questionnaire, BIPQ),⁷³ and health care service utilisation (e.g. frequency of GP follow-
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39 up or referrals, pharmacist action/s, hospitalisation(s) and emergency department admissions) will
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41 be measured between and within RCT arms at baseline and at 6-months. An evaluation of the
42
43 identification and number and type of MRPs (including side-effects), and adherence to other
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45 prescribed medication, will be undertaken at baseline and six-month follow-up.
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49 It is anticipated that the *PharMIbridge* intervention will further optimise health care utilisation
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51 by increasing pharmacist communication and collaboration with other health practitioners and other
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53 support people involved in the participant's care. The RCT will involve increased use of
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55 MedsChecks by community pharmacists for this vulnerable population. Difference in Federal
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57 Government healthcare resource use (measured as the total of primary health care services,
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laboratory tests and medications; and MBS data) will be sought from the Australian Government Department of Human Services, with participant consent.

Pharmacy staff evaluation of training

Evaluation of the B-MHFAP training will be undertaken as a standard component of this accredited course.⁷⁴ An evaluation of the *PharMIbridge* training programme in terms of its effectiveness (in comparison to B-MHFA alone) to reduce stigma and build the required skills for pharmacists to work with people living with SPMI will involve pre- and post-training questionnaires, which will be repeated at RCT conclusion. The questionnaires will collect both qualitative and quantitative data including items adapted from validated scales such as the Social Distance Scale,⁷⁵ the Mental Illness Attitude Questionnaire,⁷⁶ and the Metabolic-Barriers, Attitudes, Confidence, and Knowledge Questionnaire (M-BACK).⁷⁷ Additional questions will specifically focus on pharmacist confidence in providing MHFA,⁴⁴ willingness to provide services for mental health consumers^{14 78 79} and barriers and incentives to working with people living with SPMI.⁶

PharMIbridge service evaluation

A proportion of IG consumer participants and pharmacists will be invited to participate in a telephone interview at RCT conclusion to qualitatively explore the acceptability and impact of the *PharMIbridge* intervention. Up to five consumer participants from each RCT region will be invited for interviews (max=20) as well as one pharmacist from each pharmacy who participated in the RCT (max=24). The participant interview guide will explore topics including: i) medication adherence and current medications; ii) types of MRPs experienced and resolved; iii) health literacy in relation to psychotropic medicines; iv) changes in relationship between participants, pharmacists and other health care professionals; and, iv) satisfaction with the *PharMIbridge* intervention. An additional participant-reported experience measure will be developed and included at the end of the service delivery in the Final Health Review. A short online survey will also be developed to explore

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3 service acceptability for other health practitioners who interact with the intervention, and other
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5 pharmacy staff, e.g. pharmacy assistants.
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10 **Data collection**

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12 The RCT data collection tools and processes will be piloted prior to use (Figure 1). Data will be
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14 collected from consumer participants, pharmacy staff and other health care professionals (Table 1).
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17 Consumer participants will be required to consent to their MBS, PBS, hospitalisation and
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19 emergency department data being accessed by researchers for a period of 12-months prior to, and
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21 six-months after, enrolment in the RCT. The reason for collecting data about resource use up to 12-
22
23 months prior to the RCT is to test for baseline differences which can then be adjusted for during
24
25 analysis.
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28 Participant data collected by pharmacists will be entered directly into purpose-built IG and
29
30 CG research modules within GuildCare NG™. This cloud-based pharmacy software platform is
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32 used by the majority of community pharmacies in Australia for the delivery of professional service
33
34 programs such as MedsCheck; it also links to dispensing systems. In the IG, nominated members
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36 of the participant's treating team (i.e. GP, psychiatrist, mental health case manager) will be provided
37
38 with access to their individual consumer participant's research records to facilitate timely access to,
39
40 and exchange of, shared information.
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44 Participating community pharmacies will receive funding to support their research
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46 involvement, including an administration fee for training attendance, research administration and
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48 data management (ranging from \$3,700-\$10,712 depending on urban/rural/remote location), as well
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50 as a per-participant fee for initial and follow-up consultations, and for six-month data collection. IG
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52 pharmacies will be remunerated for the baseline data collection and Initial Health Review (75
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54 minutes; \$167), follow-up consultations (Level 1: up to three consultations; \$66, or Level 2: greater
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56 than three consultations; \$133), and for the Final Health Review and follow-up data collection (30
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3 minutes; \$167). Service fees for CG pharmacists include the MedsCheck consultation and baseline
4 data collection (60 minutes; \$133) and the six-month follow-up data collection (30 mins; \$66). A
5 gift voucher valued at AUD\$30 will be offered to all consumer participants at the final, six-month
6 data collection point in recognition of their time for completing data collection processes that would
7 not normally be part of their health care.
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17 **Sample size**

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19 Based on a recent study conducted in a similar population,⁶ we assume the baseline rate of non-
20 adherence assessed using pharmacy dispensing data will be 56%. This outcome will be available
21 for all participants (unless actively withdrawn), regardless of treatment adherence. We assume the
22 percentage of non-adherent participants in the CG arm will drop to 51% (based on the results of
23 previous studies exploring adherence as an outcome of a MedsCheck service),³⁰⁻³³ and the
24 percentage of non-adherent participants in the IG arm will drop to 35%.⁶ With $\alpha=0.05$, the RCT
25 will have 80% power to find a statistically significant difference between RCT arms with 149
26 individuals recruited to each arm (without accounting for clustering).
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38 As this is a cluster-RCT we need to account for the non-independence of observations from
39 individual participants recruited from the same pharmacy. We assume a median number of 10
40 participants at each pharmacy, and conservatively assume the $ICC=0.03$, giving a design effect of
41 1.27. Consequently, a total of 190 participants will need to be recruited in each arm (380 in total).
42 To achieve this, 10 consumer participants will need to be enrolled from each of 38 pharmacies.
43 Assuming that 20% of pharmacies will withdraw from the RCT without enrolling any participants,
44 a total of 48 pharmacies will need to be recruited.
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Data analyses

Descriptive statistics will be used; mean (standard deviation) or median (25th-75th percentile) for continuous data and frequency (percentage) for categorical data. We will compare the primary outcome of percentage adherence between RCT arms using a mixed-effects logistic regression model, with treatment arm entered as the fixed effect and pharmacy entered as a random effect, to account for possible non-independence of observations from participants who attend the same pharmacy. Results will be reported as odds ratios and 95% Wald-based confidence intervals.

For secondary analyses, interval data will be analysed using mixed-effects linear regression, binary data using mixed-effects logistic regression, and count data using mixed-effects Poisson regression models. In all cases, the likely non-independence of data from individuals enrolled through the same pharmacy will be accounted for as random effects in the regression models. Analyses will be based on the intention-to-treat principle, with participants analysed according to the treatment they were allocated to receive. Data will be analysed using Stata statistical software (StataCorp, College Station, TX, USA), with significance set at less than 0.05.

Qualitative interviews will be audio-recorded (with participant consent), transcribed verbatim and quality checked. Thematic analysis will be conducted by experienced qualitative researchers within the research team. This process involves reading and re-reading transcripts to identify, analyse and report patterns within the data, leading to the identification of similar codes across the entire data set.⁸⁰ Initial codes are thereby sorted into themes and subthemes.⁸⁰

Economic evaluation

We hypothesise that the provision of the *PharMIbridge* intervention will be cost-effective compared to standard care from a health care sector perspective with regard to RCT-based costs and outcomes (cost per additional participant adherent/cost per [proxy] health outcome). The base case analysis

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3 will comprise the cost per additional 'adherent' participant for the IG compared with the CG and
4 reported as the incremental cost-effectiveness ratio (ICER). The outcome for the base case analysis
5 is the difference in the change in the proportion of 'adherent' participants from baseline to RCT
6 conclusion, between the IG and CG. Sub-group analyses will be conducted for the primary outcome
7 measure (adherence) based on participant characteristics. Regression analyses using 'adherence' as
8 the dependent variable will be performed to assess if the effect of the intervention varies by SPMI
9 diagnosis, age, gender, pharmacy location and number of other medications taken concurrently.
10 Any evidence of non-linearity will be adjusted for using appropriate transformations.
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22 A cost per Quality Adjusted Life Year (QALY) gain will also be conducted based on health-
23 related Quality of Life data collected within the trial. QALYs will be estimated by applying
24 Australian utility weights and using the area under the curve approach. Difference in QALYs
25 between the IG and CG will be estimated using linear or non-linear regression methods depending
26 on the nature of the data. The analytical time-frame for the cost effectiveness analyses will be
27 limited to that of the follow-up period of the trial. This is the most conservative approach relative
28 to translation of the primary outcome measure, adherence, where there is likely to be heterogeneity
29 of medications and conditions.
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40 Costs will be considered from the health system perspective and include both the cost of
41 interventions and the cost consequences from potential changes in health care utilisation. The
42 difference in health resource use for all participants will be collected and analysed based on
43 administratively collected MBS, PBS and pharmacy dispensing data.
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51 Included costs

52 The difference in health resource use for all participants will be collected and analysed from their
53 MBS and PBS records six-months prior to, and during, enrolment in the RCT. Impact of seasonality
54 will also be assessed for the same 12-month period. The economic evaluation will quantify costs
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3 associated with the *PharMIbridge* intervention at a participant level in the eligible population. The
4 costs measured in the economic evaluation should be equivalent to their ‘opportunity cost’, i.e.
5 assessed in terms of the monetary value of the benefits that are foregone because the resources are
6 not available for their best alternative use. The opportunity cost will be estimated from the market
7 costs of the resources consumed, whenever available. Costs from the RCT include, but will not be
8 limited to: i) the training of pharmacists to provide the *PharMIbridge* intervention; ii) the fee-for-
9 service to pharmacists; and, iii) the clinical software adaption to facilitate the identification of ‘non-
10 adherent’ participants and record interventions.
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24 Cost data analysis

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26 The source of any variation (if observed) in costs between intervention and comparator arms, as
27 well as the cost ‘drivers’, will be investigated with a Generalised Linear Model (GLM) using a
28 standard statistical software package (STATA). As cost data are not likely to be normally
29 distributed, a gamma log-link function or similar will be used, with appropriate testing of the GLM
30 specification using the modified Park test and link test. Full costing will be provided for the RCT.
31 If certain costs are not included in the economic evaluation, any assumptions, and the effect of their
32 exclusion, will be specified in the analysis.
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42 Costing of the *PharMIbridge* intervention will be undertaken as follows: i) identify
43 administrative resources used in program management, with RCT-specific administrative resources
44 separated from activities that would be included in a national roll-out of the program; ii) some
45 resource use will be measured in natural units (for example, clinical staff time spent on delivering
46 the *PharMIbridge* intervention) and will be valued in monetary units; iii) other resources can be
47 directly valued (for example, incentive payments to staff and services); and, iv) if the *PharMIbridge*
48 intervention delivery requires additional equipment (e.g. privacy screen), market costs will be
49 estimated with amortisation applied over the useful life of the equipment.
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Sensitivity analysis

The uncertainty in effect sizes and costs will translate into a degree of uncertainty around the estimated ICER. This uncertainty will be explored using a system of seemingly unrelated regression equations. This has been chosen because it has been argued that such methods are generally robust to skewed data, and to allow for any correlation between costs and effects. The cost and adherence (or QALY) regressions will be run simultaneously, including SPMI diagnosis, age, gender, pharmacy location and number of other medications taken concurrently included (as covariates) to explore potential sub-group differences with respect to adherence, costs or cost-effectiveness. Additionally, in order to estimate the level of uncertainty associated with the decision as to whether or not the intervention was cost-effective, we will use the non-parametric bootstrap technique (with 5,000 replications sampled with replacement) to estimate the probability that the intervention is cost-effective over a range of willingness to pay per outcome (adherer / QALY) according to the cost-effectiveness acceptability curve.

Financial appraisal

Financial appraisal and full pathway costing will be undertaken as part of the *PharMIbridge* RCT. Where assumptions for identification, measurement and valuation of economic costs differ to financial costs, these differences will be specified. The cost to the health sector if the *PharMIbridge* intervention was implemented nationally will be extrapolated over a five-year time frame.

Patient and public involvement

To provide maximum benefit to people with SPMI, health services need to be relevant, accessible and responsive to their needs. The views of people with lived experience of a mental illness will be paramount to the success of the *PharMIbridge* RCT, from their involvement in the development of

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3 the RCT protocol as members of the research team, development and implementation of the
4 intervention with pharmacy staff as trainers and mentors, and as representatives on the Expert Panel
5 who will have oversight across the lifetime of the research. A working group of partner organisation
6 representatives, consumer representatives, and experts actively involved in improving mental health
7 care will co-develop training material. People with lived experience of SMPI will also inform
8 dissemination strategies based on the RCT findings.
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19 **DISCUSSION**

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21 The *PharMIbridge* RCT will use the medication expertise of community pharmacists to support
22 medication adherence and address the physical and mental health needs of participants using
23 psychotropic medication for SPMI. The focus on the physical health of people living with SPMI is
24 of utmost importance given the considerable life expectancy gap attributable to physical
25 comorbidities in this population. Beyond improved consumer participant wellbeing, the
26 *PharMIbridge* RCT is expected to facilitate better relationships between pharmacists and local
27 health services, including community mental health teams, PHNs and GPs. Lastly, by providing a
28 diverse range of mental health services and resources and by increasing community outreach to
29 mental health and non-mental health related services IG pharmacies will become more prominent
30 in the mental health sector
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44 Although the provision of a MedsCheck service for people using high-risk medication such as
45 psychotropics (in addition to other criteria), is a currently funded service, there is evidence that
46 pharmacists' mental health literacy concerning SPMI is lower in comparison to other mental
47 illnesses.⁴⁰ Most people using antipsychotics and/or mood stabilisers would be eligible for a
48 MedsCheck, however, we believe that this vulnerable population may be missing out on this service
49 as it is not specifically targeted towards mental health consumers. Therefore, the proposed
50 *PharMIbridge* intervention is a novel service within the community pharmacy setting and is, to our
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3 knowledge, the first RCT to determine the impact of a pharmacist-led support service for people
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5 living with SPMI.
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8 All pharmacy staff involved in the RCT will receive B-MHFA. Hence, the *PharMIbridge* RCT
9
10 provides an opportunity for all consumer participants to access a recognised standard level of care.
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12 Furthermore, analyses conducted on the CG consumer participant outcomes will allow us to identify
13
14 the impact of MedsCheck for consumers living with SPMI. This is particularly important given the
15
16 current lack of data regarding the impact of MedsChecks on medication adherence. Furthermore, it
17
18 is unrealistic and unethical to expect that consumer participants living with SPMI and enrolled into
19
20 the CG receive no form of care or service. These participants will be asked to complete a range of
21
22 surveys at baseline which are likely to identify adherence and health issues, and consequently
23
24 pharmacists would be expected, as health care professionals, to intervene in such situations. Thus,
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26 the research team also anticipates positive outcomes for CG participants, although this effect is
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28 hypothesised to be inferior to IG participants.
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34 There are some limitations to this RCT. While a key focus of this research is the physical health
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36 care needs of consumer participants, the follow-up time of six-months is insufficient to use physical
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38 health as a primary outcome measure. The RCT duration was selected to meet the specified time-
39
40 frame requirements of the funding body. Hence, the long-term impact of the *PharMIbridge*
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42 intervention cannot be determined. It should be noted that the RCT sites, while specifically chosen
43
44 to reflect a variety of geographical regions, types of pharmacies, mental health services and socio-
45
46 economic factors, may not be generalisable to the Australian population. Lastly, as adherence is
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48 known to be an inherently difficult concept to measure, to ensure accurate and comprehensive
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50 assessment the research team will use multiple objective and subjective measures to assess this
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52 outcome. Notwithstanding these limitations, the *PharMIbridge* RCT will provide valuable insights
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54 into the future implementation of a community pharmacy-based, mental health support service
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56 across Australia.
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Ethics and dissemination

This RCT protocol and training program has been approved by Griffith University Human Research Ethics Committee (2019/473 and 2019/493). The trial has been registered with the Australia and New Zealand Clinical Trials Registry (ANZCTR #). At the conclusion of the *PharMIbridge* RCT, a report will be submitted to the Australian Government Department of Health and partner organisations. A dissemination plan will be developed by the research team, project partners and the Expert Panel. A summary of findings for all participating pharmacies and consumer participants will be provided at the end of the RCT. Results will be published as manuscripts in peer-reviewed journals and presented at national and international scholarly conferences and symposia.

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Contributors AW, COR, SM and SE designed the research protocol and were named investigators on the funding proposal. AW and COR are co-principal investigators and led the intervention and training development and evaluation plan. JB provided expert oversight of the economic evaluation plan, assisted with the selection of primary outcome measures and datasets. SM and SE led the ethics application process, review of data collection tools and contributed to the intervention and training development and evaluation plan. RW provided statistical expertise and sample size calculations for the RCT. All authors were involved in the revision of this protocol and made a significant contribution towards its intellectual content and approved the final version of the manuscript.

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3 **Competing interests** None declared.
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6 **Patient Consent** Not required.
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9 **Ethics approval** Griffith University Human Research Ethics Committee (HREC/2019/473 and
10 HREC/2019/493).
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14 **Provenance and peer review** Not commissioned; peer reviewed for ethical and funding approval
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Table 1: Data collection

Type of evaluation	Description/measure	Data source	Time-point in weeks (RCT)		
			Before RCT	0	26
Formative	Training evaluation (paired pre- and post-questionnaires)	Pharmacists in IG and CG			
Adherence	MPR and medicine persistence RAM ⁵² scale	Pharmacy			
		PBS data			
		GuildCare NG TM documentation (all consumer participants)			
Medication outcomes	Identification of MRPs and management (MedsCheck or DOCUMENT system ⁸¹)	GuildCare NG TM documentation (all consumer participants)			
Goal achievement	Type and number of goals set, goal achievement (GAS) ⁶⁷	GuildCare NG documentation (IG consumer participants)			
Clinical measurements	Clinical measures for each consumer participant - Weight / Height (Body Mass Index) - Abdominal girth - Blood pressure	GuildCare NG TM documentation (all consumer participants)			
		Prescribers / other health workers			
Health and related outcomes	- PAVS, ⁵⁶ Dietary Behaviour, ⁵⁷ ASSIST ^{58,59} AQoL-6D, ⁶⁸ ISI, ⁶⁹ MTBQ, ⁷⁰ DAI-10, ^{71,72} BIPQ, ⁷³ K6 ⁸² - M3Q ⁶⁰ SIMPAQ, ^{61,62} PSQI, ⁶³ Fagerström Test for Nicotine Dependence, ⁶⁴ BPI ^{65,66}	- GuildCare NG TM documentation (all consumer participants)			
		- IG consumer participants only			
Impact	- Consumer reported experience measure - Semi-structured interviews (service implementation, acceptability) - Online survey (service acceptability)	- IG consumer participants only			
		- IG consumer participants (n=20), IG pharmacists (n=24) - Other health care professionals (e.g. GP, psychiatrist, MH case manager) and IG pharmacy staff			
	Health care utilisation	Primary care, MBS, hospitalisation			
Economic appraisal	RCT-based economic evaluation (e.g. resources, incentive payments, time) Cost-effectiveness (health-care sector perspective)	Cost of intervention, MBS, PBS, pharmacy dispensing data			
		AQoL-6D ⁶⁸			
		Cost per additional adherer Cost per additional quality adjusted life year			

Hospitalisation, Emergency department admissions, MBS and PBS data will be obtained for 12-months before, and the entire duration of the RCT. Health outcomes data and prescription dispensing data will be obtained for the entire length of the RCT. Abbreviations: ASSIST=Alcohol Smoking and Substance Involvement Screening Test; AQoL-6D=Assessment of Quality of Life; BIPQ = Brief Illness Perception Questionnaire; DAI-10 = Drug Attitude Inventory 10; DOCUMENT=Drug selection, Over/Under dose, Compliance, Untreated indications, Monitoring, Education or information, Non-clinical, Toxicity or adverse reactions; GAS=Goal Attainment Scale; ISI=Insomnia Severity Index; K6=Kessler Psychological Distress Scale; M3Q=My Medicines and Me Questionnaire; MPR=Medicine Possession Ratio; MTBQ=Multimorbidity Treatment Burden Questionnaire; PAVS=Physical Activity Vital Sign Questionnaire; BPI=Brief Pain Inventory; PSQI=Pittsburgh Sleep Quality Index; RAM=Reported Adherence to Medicine Scale; SIMPAQ=Simple Physical Activity Questionnaire.

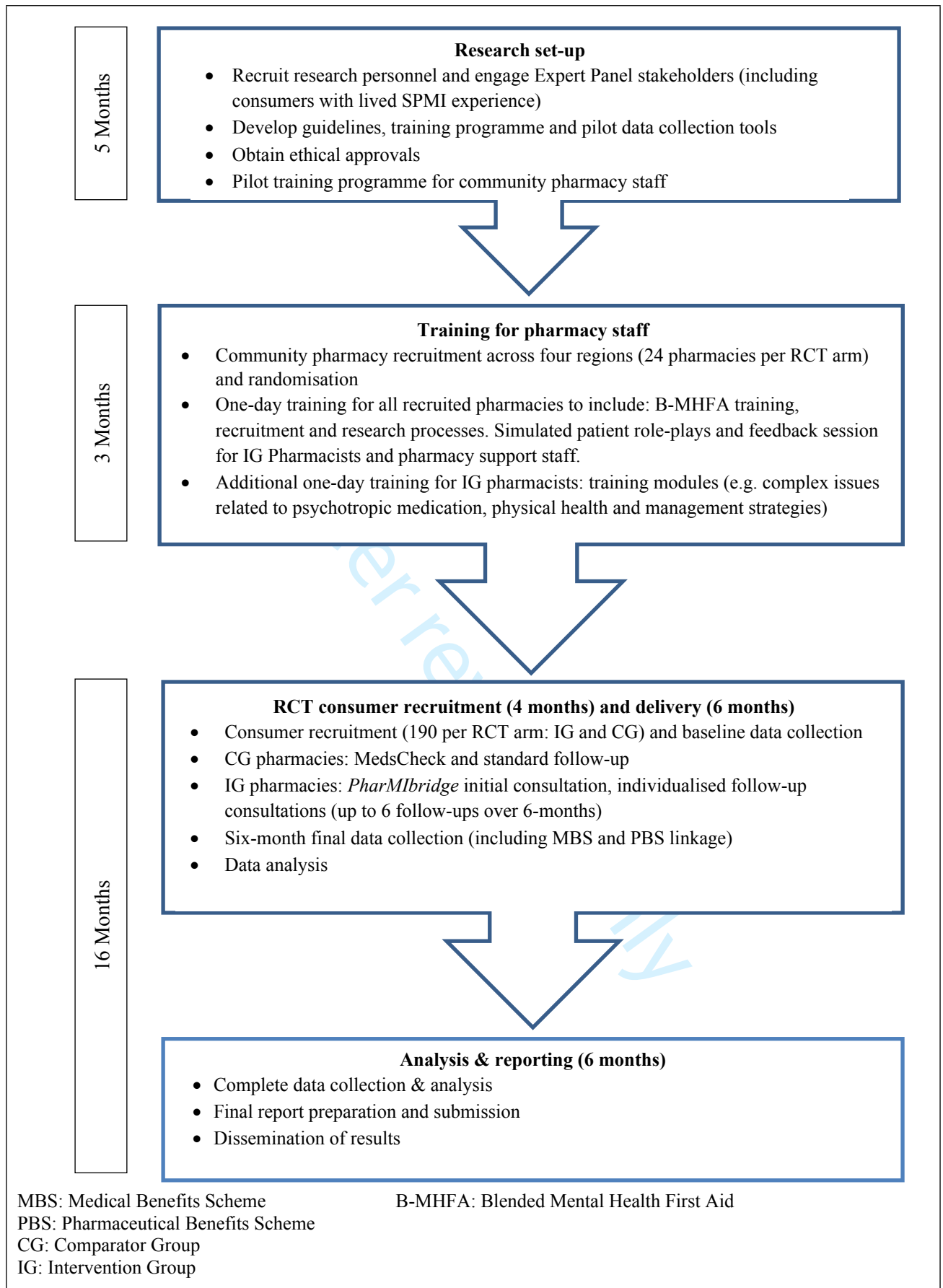


Figure 1: Overview of the research stages and timing

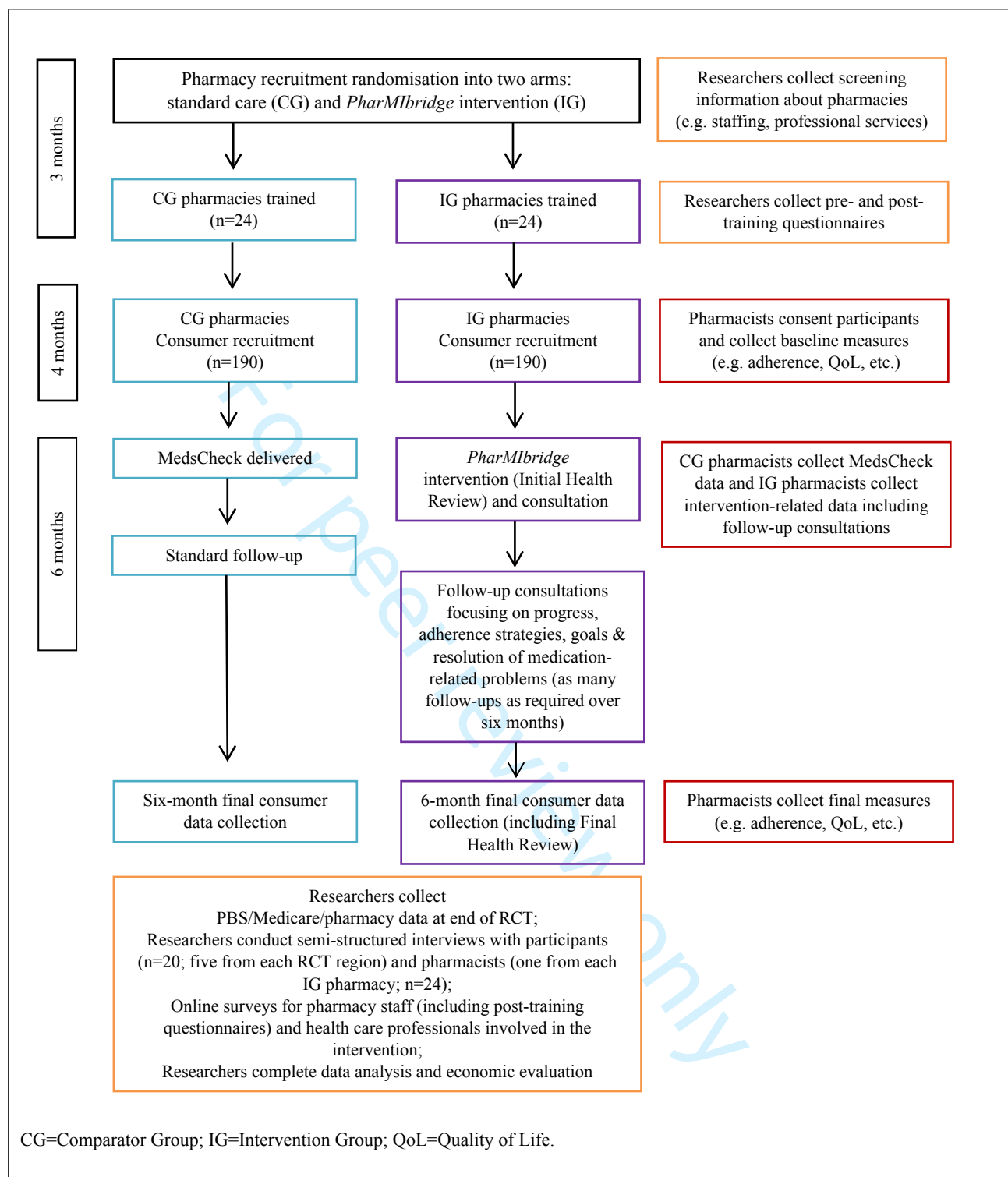


Figure 2: Overview of the *PharMIbridge* RCT

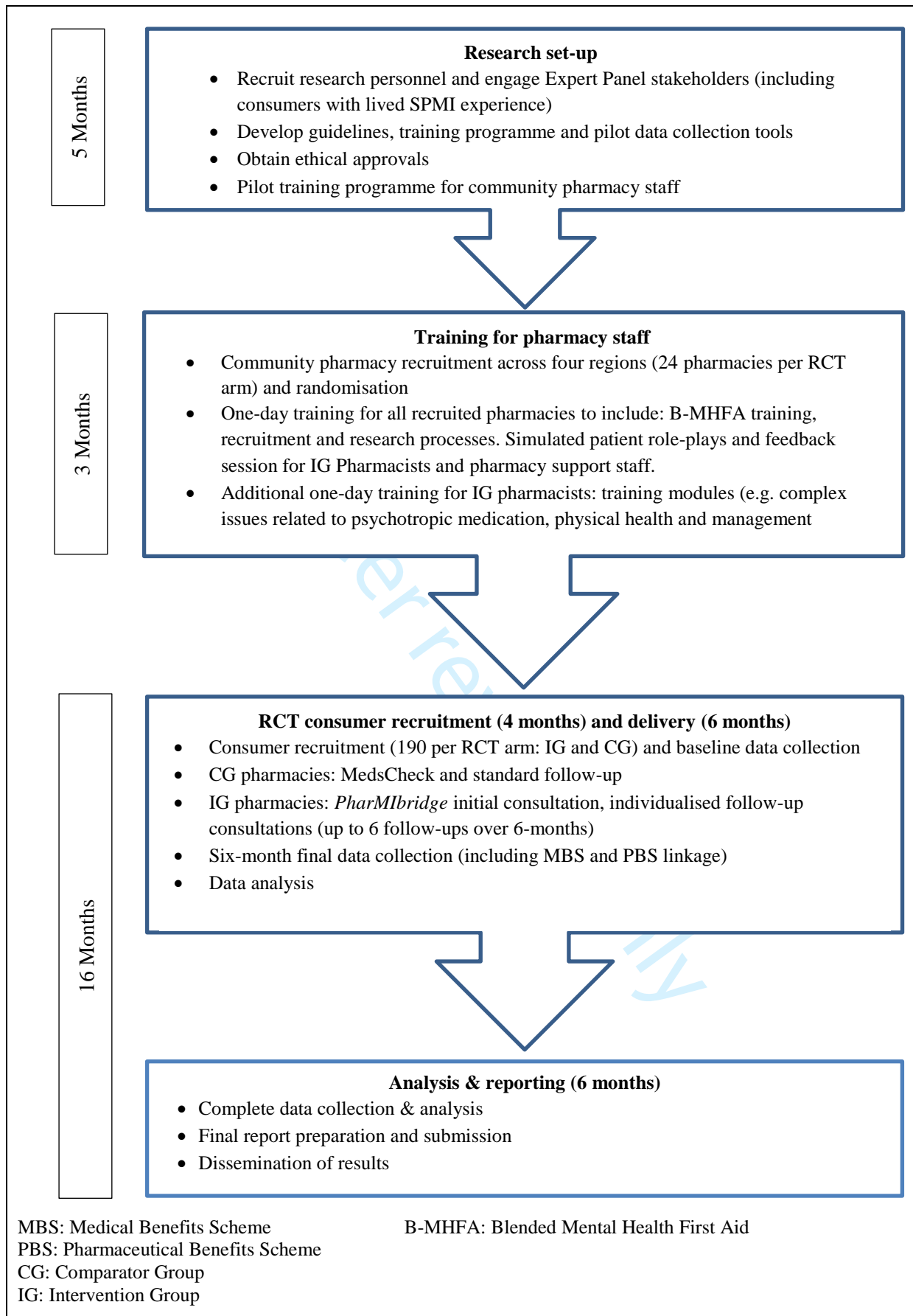


Figure 1: Overview of the research stages and timing

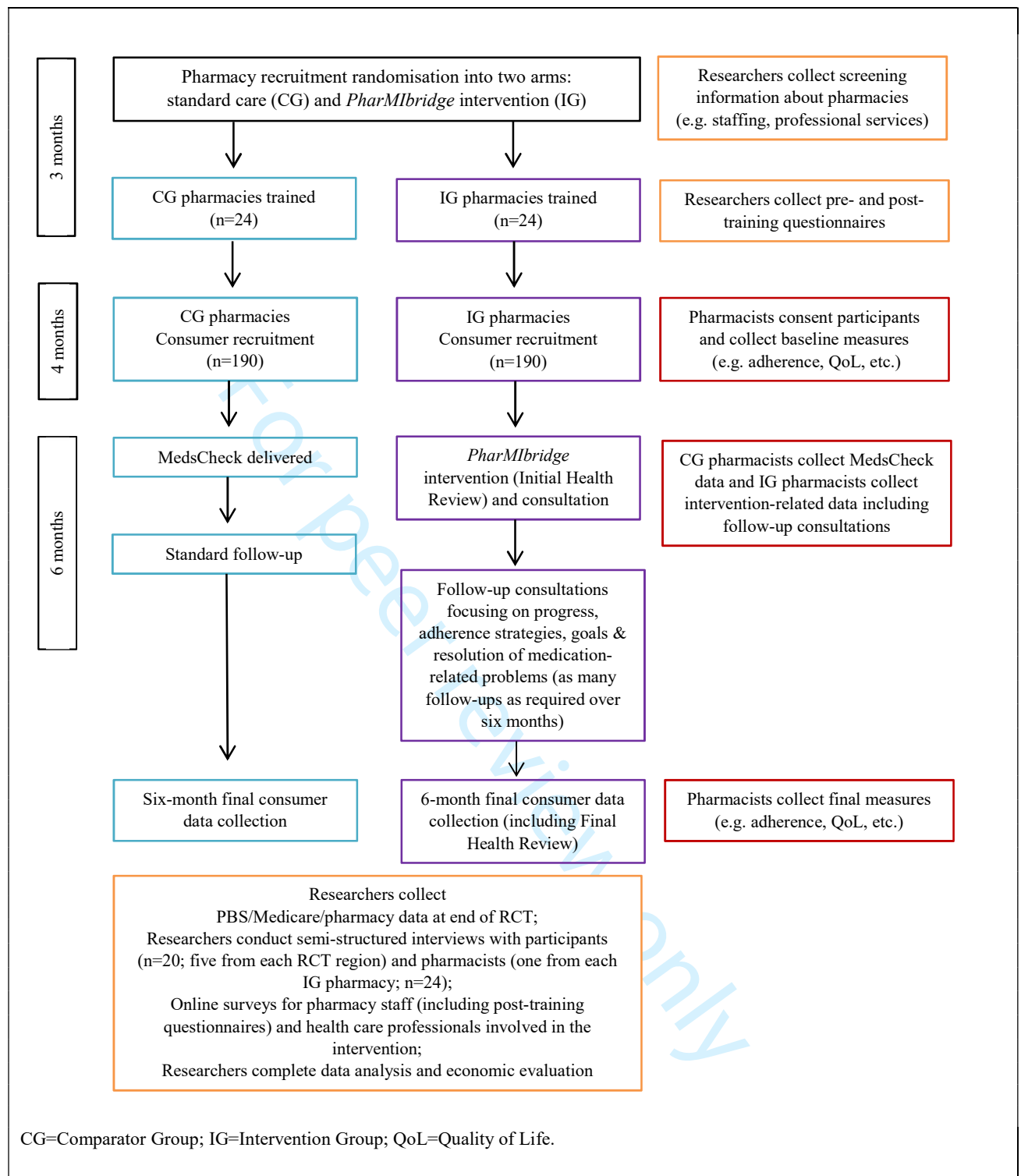


Figure 2: Overview of the *PharMIbridge* RCT



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
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1			
2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
4	mechanism		describing any steps to conceal the sequence until interventions are
5			assigned
6			
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
8			and who will assign participants to interventions
9			
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
11	(masking)		participants, care providers, outcome assessors, data analysts), and
12			how
13		17b	If blinded, circumstances under which unblinding is permissible, and
14			procedure for revealing a participant's allocated intervention during
15			the trial
16			
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Methods: Data collection, management, and analysis

20			
21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
22	methods		trial data, including any related processes to promote data quality (eg,
23			duplicate measurements, training of assessors) and a description of
24			study instruments (eg, questionnaires, laboratory tests) along with
25			their reliability and validity, if known. Reference to where data
26			collection forms can be found, if not in the protocol
27		18b	Plans to promote participant retention and complete follow-up,
28			including list of any outcome data to be collected for participants who
29			discontinue or deviate from intervention protocols
30			
31	Data	19	Plans for data entry, coding, security, and storage, including any
32	management		related processes to promote data quality (eg, double data entry;
33			range checks for data values). Reference to where details of data
34			management procedures can be found, if not in the protocol
35			
36	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
37	methods		Reference to where other details of the statistical analysis plan can be
38			found, if not in the protocol
39		20b	Methods for any additional analyses (eg, subgroup and adjusted
40			analyses)
41		20c	Definition of analysis population relating to protocol non-adherence
42			(eg, as randomised analysis), and any statistical methods to handle
43			missing data (eg, multiple imputation)
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Methods: Monitoring

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53	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
54			and reporting structure; statement of whether it is independent from
55			the sponsor and competing interests; and reference to where further
56			details about its charter can be found, if not in the protocol.
57			Alternatively, an explanation of why a DMC is not needed
58			
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2		21b	Description of any interim analyses and stopping guidelines, including
3			who will have access to these interim results and make the final
4			decision to terminate the trial
5			
6	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
7			spontaneously reported adverse events and other unintended effects
8			of trial interventions or trial conduct
9			
10			
11	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
12			whether the process will be independent from investigators and the
13			sponsor
14			

Ethics and dissemination

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16			
17	Research ethics	24	Plans for seeking research ethics committee/institutional review board
18	approval		(REC/IRB) approval
19			
20			
21	Protocol	25	Plans for communicating important protocol modifications (eg,
22	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
23			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
24			regulators)
25			
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial
27			participants or authorised surrogates, and how (see Item 32)
28			
29		26b	Additional consent provisions for collection and use of participant data
30			and biological specimens in ancillary studies, if applicable
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33	Confidentiality	27	How personal information about potential and enrolled participants will
34			be collected, shared, and maintained in order to protect confidentiality
35			before, during, and after the trial
36			
37	Declaration of	28	Financial and other competing interests for principal investigators for
38	interests		the overall trial and each study site
39			
40			
41	Access to data	29	Statement of who will have access to the final trial dataset, and
42			disclosure of contractual agreements that limit such access for
43			investigators
44			
45	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
46	post-trial care		compensation to those who suffer harm from trial participation
47			
48	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
49	policy		participants, healthcare professionals, the public, and other relevant
50			groups (eg, via publication, reporting in results databases, or other
51			data sharing arrangements), including any publication restrictions
52			
53			
54		31b	Authorship eligibility guidelines and any intended use of professional
55			writers
56			
57		31c	Plans, if any, for granting public access to the full protocol, participant-
58			level dataset, and statistical code
59			
60			

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

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BMJ Open

Bridging the gap between physical and mental illness in community pharmacy (PharMIbridge): protocol for an Australian cluster randomised controlled trial

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3 **Title: Bridging the gap between physical and mental illness in community pharmacy**
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5 **(PharMIbridge): protocol for an Australian cluster randomised controlled trial**
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ABSTRACT

Introduction There is a significant life expectancy gap attributable to physical comorbidities for people living with severe and persistent mental illness (SPMI) compared to the general population. Medications are a major treatment for SPMI management and physical illnesses, hence pharmacists are well-positioned to support mental healthcare and comorbidities. The RCT aim is to evaluate effectiveness of an individualised, pharmacist-led, support service for people experiencing SPMI focusing on medication adherence and physical comorbidity management, compared to standard care (a medication-management service; MedsCheck).

Methods and analysis *PharMIbridge* is a cluster RCT, whereby community pharmacies in four Australian regions will be randomised (1:1 ratio), to either Intervention Group (IG) or Comparator Group (CG). All IG and CG pharmacy staff will receive Blended-Mental Health First Aid training. Additionally, IG pharmacists will receive further training on medication adherence, goal setting, motivational interviewing, managing physical health concerns and complex issues relating to psychotropic medication. CG pharmacists will not receive additional training, and will provide standard care (MedsCheck). The primary outcome will be change in participants medication adherence for psychotropic medication over 6-months. Using mixed-effects logistic regression model and a cluster size of 48 pharmacies, a total of 190 participants will need to be recruited to each arm to find a statistically significant difference in medication adherence. Secondary outcomes will be changes in factors associated with cardiometabolic risk and quality of life, emphasising physical and psychological wellbeing; medication-related problems; adherence to other prescribed medication; pharmacists knowledge, confidence and ability to support people experiencing SPMI; and effects on healthcare utilisation. A within RCT-based economic evaluation comparing the intervention with standard care will be undertaken.

Ethics and dissemination The protocol and pharmacist training program received Griffith University Human Research Ethics Committee approval (HREC/2019/473 and HREC/2019/493 respectively). Results will be published in peer-reviewed journals and available at Sixth Community Pharmacy Agreement website (<http://6cpa.com.au/about-6cpa/>).

Trial Registration Number: ANZCTR12620000577910

Strengths and limitations of this study

- The *PharMIbridge* RCT builds on previous Australian research to test the effectiveness of a pharmacist-led medication support service for consumers living with SPMI, with an additional focus on the management of physical comorbidities which are highly prevalent in this population.
- A multi-disciplinary approach will encourage participating pharmacies to develop and maintain working relationships with local GP clinics, medical centres, mental health care teams, and other physical health/exercise centres and practitioners (e.g. gyms) beyond the life of the RCT.
- Routinely collected pharmacy dispensing and Pharmaceutical Benefits Scheme (PBS) data will be used, alongside self-reported measurements, to evaluate medication adherence, which is the primary outcome measure.
- While a key focus of this RCT is exploring the impact of the *PharMIbridge* intervention on the physical wellbeing and overall health of people living with SPMI, the follow-up time is insufficient to use these and related outcomes as primary outcome measures.
- It is not possible for pharmacy staff or consumer participants to be blind to service allocation, due to the nature of the intervention.

BACKGROUND AND RATIONALE

Community pharmacists are highly trusted and essential members of the primary healthcare team, playing a vital role through medication supply and information provision. Given the accessibility of community pharmacies, pharmacists are in an ideal position to adopt a triage-style role, signposting to other health care professionals and services. There is an emerging role, and growing need, for community pharmacists to support and manage mental illnesses. Research has demonstrated that pharmacists are capable of identifying consumers at risk of depression and referring appropriately for diagnosis and therapy,¹⁻³ managing psychotropic (e.g. antipsychotic and mood stabiliser) medication-related problems (MRPs),⁴⁻⁷ providing antidepressant adherence support, and working within multidisciplinary mental health care teams.⁸⁻¹⁰

However, evidence also suggests that health care professionals, including pharmacists, are not exempt from holding stigmatising attitudes and behaviours towards mental health consumers;^{11 12} pharmacists with more marked stigmatising attitudes were reported to be less willing to provide professional services to people with severe and persistent mental illness (SPMI)*.¹⁴ Lack of training in mental health or the opportunity to acquire the necessary skills and confidence in working with mental health consumers, have been cited as barriers to providing appropriate and timely care for this population.¹⁵ Hence, the urgent need to develop a training program that addresses pharmacists' mental health knowledge gaps in anticipation of improving attitudes towards, and confidence in, providing care for people living with SPMI. This is particularly important in the Australian context given that 61.5% of people who experience psychosis, do so on multiple occasions, with partial or complete remission of symptoms between episodes.¹⁶ Also of relevance is that a substantial proportion of Australians

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2
3 using psychotropic medications access health care services in community settings, with 39-
4 million mental health-related prescriptions dispensed in Australia in 2018-19.¹⁷
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8 Of significant concern is that Australians living with SPMI also experience poor physical
9 health; they are five times more likely to smoke, six times more likely to die from
10 cardiovascular disease and four times more likely to die from respiratory disease than the
11 general population, leading to a 14-23 year gap in life expectancy.¹⁸ These issues are often
12 overlooked and/or dismissed by health care professionals and policy makers.¹⁹ For example, a
13 study by Morant et al.²⁰ in the United Kingdom found that the physical health concerns of
14 antipsychotic users were not addressed by prescribing psychiatrists. Decisive action is needed
15 to engage both relevant health practitioner groups and people living with SPMI with respect to
16 physical health management.²¹
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29 The acceptability of medications by people living with SPMI is also problematic and
30 adherence is poor.²² Reasons include, but are not limited to, experiencing (or the risk of
31 experiencing) unwanted side effects, reluctance to rely on medication, and forgetfulness.²² Poor
32 adherence with antipsychotics is a key reason for relapse in psychosis; even missing a few days
33 of treatment substantially increases this risk.²³ However, a good therapeutic relationship with
34 attending health practitioners is linked to better medication adherence, fewer hospital
35 admissions and a reduction in self-harm in people experiencing psychosis.²⁴ In this respect,
36 pharmacist-led medication reviews for mental health consumers have shown promising
37 results,^{7 25} and given the associated concerns with drug-drug interactions, are particularly
38 relevant for those living with SPMI using psychotropic medications.
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54 **Evidence gap**

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56 Overall, there is relatively limited research on improving outcomes for consumers living with
57 SPMI in the primary care setting (including community pharmacy). Whilst research exploring
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3 the impact of medication reviews on psychotropic prescribing within residential aged care
4 settings has been conducted,²⁶ few studies have involved participants using psychotropic
5 medications living in the community,^{27 28} particularly those experiencing SPMI.²⁹ While
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10 Australian pharmacists can provide a medication review service in the form of a MedsCheck[†]
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12 within the community pharmacy setting, research exploring the impact of this service on
13
14 medication adherence is limited.³⁰⁻³³
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17 To our knowledge, research exploring the impact of a community pharmacist-delivered
18 medication or health-related service specifically for people living with SPMI is scarce. A
19 Canadian study demonstrated that pharmacy staff supported mental health consumers by
20 providing follow-up care which focused on medication management and improving health
21 service navigation and most study participants were using multiple psychotropic medications,
22 few were living with SPMI (n=36; 17.9%).^{34 35} Additionally, results from an Australian
23 community-based, pharmacist-led medication support service for participants living with
24 depression and anxiety were positive with significant improvements in relation to participants
25 illness perceptions, medication satisfaction and medication adherence.⁶ Our proposed
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Randomised Controlled Trial (RCT) builds and expands on this evidence to test the
effectiveness of a person-centred, goal-oriented, and flexible, pharmacist-led support service
for people living with SPMI, with a specific focus on improving medication adherence and
managing physical comorbidities. For the purpose of this RCT, SPMI refers to any mental
illness that has a continuous and significant effect on a person's daily life, and includes (but is
not limited to) the following: schizophrenia and other psychotic disorders, severe and recurrent
depression, and bipolar disorder.

[†]A MedsCheck is an Australian remunerated service which involves a community pharmacist reviewing a person's medication, identifying any medication-related problems (MRPs), and providing related medication information. Australian residents eligible for a MedsCheck service include consumers who are at a higher risk of MRPs, such as those using more than five prescription medicines.³⁰

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Study objectives

The aim of this RCT is to evaluate the effectiveness of “Bridging the Gap between Physical and Mental Illness in Community Pharmacy (*PharMIbridge*)”; an intervention comprising an individualised, pharmacist-led, support service for people living with SPMI, compared to standard care involving a one-off medication management service (MedsCheck). The primary objective is to test the impact of the *PharMIbridge* intervention (Intervention Group; IG) on psychotropic medication adherence. It is hypothesised that the *PharMIbridge* intervention will demonstrate a 20% increase in adherence at six-months compared with standard care (Comparator Group; CG). Overall, the objectives of the *PharMIbridge* RCT are to assess changes in:

- medication adherence (for psychotropic and other prescribed medication);
- health outcomes including quality of life, physical health and psychological wellbeing;
- community pharmacists’ confidence, knowledge and ability to address the medication-related and physical health care needs of people living with SPMI; and,
- health care service acceptability, utilisation and cost-effectiveness

The findings will be used to inform a more widespread implementation of person-centred service models for people living with SPMI within the primary healthcare sector.

METHODS

Using a cluster RCT design, community pharmacies will be randomised to deliver either:

- i) the *PharMIbridge* intervention; or,
- ii) standard care involving a one-off MedsCheck service.

Figure 1 provides an overview of the research design, which involves a partnership between two University institutions (Griffith University and The University of Sydney) and

1
2
3 two professional pharmacy organisations (The Pharmacy Guild of Australia and The
4 Pharmaceutical Society of Australia). Genuine engagement throughout the entire RCT with
5 individuals with lived experiences of SPMI is critical to success. Given that those living with
6 SPMI require a multifaceted approach to meet their mental and physical health care needs, a
7 multidisciplinary team is also a key component of the *PharMIbridge* RCT. An Expert Panel
8 will be formed, with invitations extended to consumer representatives living with SPMI, and
9 representatives from key organisations such as Mental Health Australia, National Mental
10 Health Consumer and Carer Forum, Sane Australia, the Royal Australian and New Zealand
11 College of Psychiatrists (RANZCP), and the Royal Australian College of General Practitioners
12 (RACGP). The Expert Panel will provide the research team with guidance on the
13 implementation of the RCT, including advice on consumer and healthcare professional
14 engagement, training materials and other resources, and research translation. The research team
15 will work with local Primary Health Networks (PHNs)[‡] across RCT sites to recruit eligible
16 community pharmacies into the *PharMIbridge* RCT.
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[‡] PHNs are independent organisations funded by the Australian Government. They work closely with local hospital networks and each PHN is overseen by a board of medical professionals. PHNs conduct assessments of the health needs of their region to identify groups of people who need more resources, programs and services. The information helps PHNs to tailor health services to meet the community's needs (<https://www.healthdirect.gov.au/primary-health-networks-phns>). 8

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Insert Figure 1 about here

Study setting and population

This RCT will be conducted in four Australian regions including urban, rural and remote. Two regions in Western Australia (WA) (i.e. South-West and Metropolitan/South Perth), one region in New South Wales (NSW) (i.e. Hunter New England) and the Australian Capital Territory (ACT) will be included. RCT sites will include a mix of community pharmacies within varied PhARIA (Pharmacy Accessibility/Remoteness Index of Australia classification) locations,³⁶ while also ensuring pharmacies ability to meet the eligibility criteria and recruit the required number of consumer participants. For example, the South-West region of WA includes a mix of regional and remote areas and has a high need for mental health services, with only 6% of the affected population reported to be receiving appropriate care for their mental health problems.³⁷

Community pharmacies

Community pharmacies located within the selected RCT regions will be eligible if they have:

- i) approval to dispense pharmaceutical benefits as part of the Pharmaceutical Benefits Scheme (PBS);
- ii) accreditation for Quality Care Pharmacy standards (quality assurance program for community pharmacies);
- iii) a clientele demographic that includes people with SPMI;
- iv) routinely provided MedsCheck as an established professional service;
- v) guaranteed that the *PharMIbridge* intervention will be carried out by a registered pharmacist who has completed the training;
- vi) a private room/area for confidential conversations and assessments;
- vii) pharmacy owner/manager consent to participate; and,

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3 viii) an established working relationship with local GP clinics or centres, mental health
4 care teams, and/or are already engaged with mental health promotion.
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8 Pharmacies will be randomised into the IG or CG after stratification by region and
9
10 geographic location (urban/rural/remote). Within each stratum, pharmacies will be randomly
11
12 allocated in a ratio of 1:1 to the IG or CG. Randomisation will occur after all pharmacies for
13
14 that RCT region have been recruited. The number of full-time equivalent employees will be
15
16 ranked within each stratum, and pharmacies will be formed into pairs. A list of computer-
17
18 generated random numbers will be used to allocate either the PharMIbridge intervention (IG)
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20 or MedsCheck service (CG) to the first of each pair; the second in each pair will be allocated
21
22 the alternative service. It is expected that 12 pharmacies will be located in urban, nine in
23
24 regional/rural and three in remote areas in each of the RCT arms.
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30 31 Consumer participants

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33 Trained pharmacy staff (CG and IG) will identify ten eligible consumers per pharmacy for an
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35 enrolment period of six months. Consumers can also self-identify into the RCT via research
36
37 promotion or be referred directly from a treating health care professional, non-government
38
39 organisation or mental health service. Eligible consumers need to have capacity to provide
40
41 informed consent, as assessed by trained pharmacy staff using capacity assessment principles
42
43 for RCT participation, and consent to pharmacists contacting their treating healthcare team
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45 (e.g. GP, case manager, psychiatrist).³⁸ Furthermore, eligible consumers need to provide
46
47 consent to allow the researchers to access their associated Medicare Benefits Schedule (MBS),
48
49 PBS, hospitalisation and emergency department records for a 12-month pre- and 6-month post-
50
51 trial period. Specifically, eligibility will require participants to:
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53

- 54 i) be 16 years and over and residing in the community;
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3 ii) be using at least one antipsychotic or mood stabiliser for at least six-months
4 continuously, for the treatment of SPMI; and,
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7
8 iii) have a complex medication need (e.g. adherence concerns) or unmanaged physical
9 health problems.
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12 Although participants need 6-months of dispensing data for a psychotropic medicine
13 prior to RCT enrolment, medication changes during this time are reasonable, as well as the use
14 of other medication(s) for their mental and physical health. Exclusion criteria include:
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16
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- 18
19 i) aged under 16 years;
20
21 ii) unstable mental health symptoms or deemed as an unsuitable RCT participant by
22 their treating health care professionals, pharmacist or carer;
23
24 iii) ‘when required’ or inconsistent use of antipsychotic and/or mood stabiliser
25 medication(s);
26
27 iv) using an antipsychotic or mood stabiliser medication for treatment of an illness not
28 related to SPMI (e.g. off-label use of quetiapine for sleep or anxiety);
29
30 v) not consenting to participate to the researchers contacting their treating healthcare
31 practitioner, or to accessing PBS, MBS and hospitalisation data; and,
32
33 vi) receiving a MedsCheck or Home Medicines Review (HMR)[§] within 12-months
34 prior to RCT enrolment.
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***PharMIbridge* intervention**

An overview of the proposed *PharMIbridge* RCT is illustrated in Figure 2. The intervention will be undertaken by trained community pharmacists randomised into the IG. In addition to the standard care available in all community pharmacies, the intervention will provide IG consumer participants with an in-depth service that is goal-oriented, flexible and individualised. Goals will be guided by an in-depth medication review, various self-assessment questionnaires and tools (documented during the Initial Health Review consultation) and be tailored to meet individual needs. There will be a specific focus on overcoming barriers to medication adherence and addressing physical health concerns (Table 1). RCT questionnaires and tools are reported under *Study outcomes*.

Insert Figure 2 about here

IG consumer participants will receive individualised care and support over a six month period (Figure 2) to promote medication adherence, optimise the management of their mental illness, and encourage lifestyle and pharmacological strategies to improve physical health, with a particular focus on reducing cardiometabolic risk. During the initial consultation (Figure 2), IG pharmacists will utilise motivational interviewing techniques to determine participants' key concerns regarding their medication, adherence, and physical and psychological wellbeing. Upon identification of three to five key issues, IG pharmacists will: i) engage participants in a goal-setting discussion and explore strategies to achieve these goals; ii) complete a signed agreement of the support plan; and iii) confirm participant's consent to discuss this plan with their nominated healthcare professional (e.g. GP, psychiatrist, case manager, etc.). The pharmacist will continue to work with the participant over the 6-month intervention period towards goal achievement, with follow-ups as identified with the participant and in their preferred modality (face-to-face, email, telephone, text messaging). At a minimum, it is expected that participants will have at least three face-to-face consultations with IG pharmacists (including the Initial and Final Health Review consultations). However, additional

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3 consultations can occur during the RCT period and participants can obtain pharmacist advice at any
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5 time, as needed. At the final 6-month follow-up the IG pharmacist and participant will complete the
6
7 Final Health Review.
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10 IG pharmacists will be required to keep accurate records of interactions and outcomes using a
11
12 cloud-based software platform (GuildCare NG™), which is currently used in many community
13
14 pharmacies when delivering professional services. Support plans, medication-related reports and
15
16 follow-up consultations, recorded as part of the *PharMIbridge* intervention, will be accessible to a
17
18 participant's nominated health care professional for their direct input, through GuildCare NG™. IG
19
20 pharmacists will work collaboratively with participants' nominated healthcare practitioner(s),
21
22 updating them regularly via the Guildcare platform and usual communication mechanisms
23
24 especially when there are any concerns needing rapid intervention.
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30 31 **Comparator arm**

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33 Participants recruited by a CG pharmacy will receive a standard MedsCheck service after enrolment
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35 and then continue to receive the usual care that the community pharmacy provides. All requirements
36
37 outlined for the MedsCheck service will be followed, noting that some participants may not have
38
39 otherwise been eligible for this government funded service (e.g. not taking five or more medicines).
40
41 Pharmacists will schedule a follow-up consultation to complete final RCT outcome assessments
42
43 with participants six-months following recruitment into the RCT.
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49 50 **Training**

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52 Previous evidence-based programs will inform the development of the education and training
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54 materials for the RCT. This includes the training modules used in the Australian mental health
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56 feasibility study,³⁹ as well as research into pharmacists' knowledge and mental health literacy,⁴⁰
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3 mental health stigma,^{14 41} Mental Health First Aid[#] (MHFA),⁴² simulated patient assessments,^{43 44}
4
5 consumer-led education,⁴⁵ consumer perspectives and consumer/carer trainers.⁴⁶⁻⁴⁸ A training
6
7 working group will oversee and develop the training content required to deliver the intervention.
8
9
10 This group will comprise representation from content experts, consumer representatives and the
11
12 partner organisations. Face and content validity of all newly developed training material will be
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14 ensured through collaborations with mental health consumers, the multidisciplinary Expert Panel
15
16 and professional pharmacy and mental health organisations. Training will be delivered in such a
17
18 way that it facilitates a naturalistic approach to enable pharmacists to use their discretion to
19
20 individually tailor the *PharMIbridge* intervention for each participant.
21
22

23
24 Training will involve a one or two-day program depending on RCT arm allocation, with IG
25
26 pharmacists attending both training days:
27

- 28 • First training day

29
30 Pharmacy staff in both IG and CG arms will complete Blended MHFA for Pharmacy (B-MHFAP)[≠]
31
32 training, involving a six-hour online module completed prior to attending the half-day face-to-face
33
34 training component.⁴⁹ It will be delivered by an accredited instructor and is certified for 24
35
36 Continuing Professional Development points. Training on research processes, including participant
37
38 recruitment and consent, service delivery, and use of GuildCare NGTM as a platform for all data
39
40 collection, will be delivered to both IG and CG pharmacy staff in separate groups to ensure they are
41
42 ‘research-ready.’ Established guidelines for providing MedsCheck services will be utilised by CG
43
44 pharmacists.⁵⁰ A standard operating procedure (SOP) will be provided to all pharmacists outlining
45
46 the various steps in the research process.
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51 The remainder of the first day of training for IG pharmacy staff will involve the use of
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53 simulated patient role-plays with the accredited B-MHFAP instructors and mental health consumers
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60 [≠] The blended MHFA in the Pharmacy (B-MHFAP) course uses case-studies, videos and resources tailored to pharmacy staff learning needs and is completed in a blended format, combining eLearning and a follow-up 4-hour face-to-face session.
<https://mhfa.com.au/courses/public/types/blendedpharmacy>

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3 to encourage staff to practice their newly acquired MHFA skills.^{43 44 51} Simulated patient role-plays
4
5 with on-the-spot performance feedback will allow pharmacy staff to demonstrate their newly
6
7 acquired skills in a safe, authentic and supportive learning environment. Research has highlighted
8
9 the importance of behavioural assessments post-training due to the potential for over, and/or under,
10
11 estimating skills through self-reported measures.⁴³ Research has also indicated that both participants
12
13 and observers of simulated B-MHFAP role-plays report higher self-reported confidence than those
14
15 who receive MHFA only, and that maintain improvements in confidence post-training.⁴⁴
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19 • Second training day

20
21 IG pharmacists will be required to complete four interactive training modules on key issues
22
23 associated with psychotropic medication use and physical health, and how to address these issues
24
25 for people living with SPMI, using evidence-based tools. The modules will be developed by the
26
27 training working group and led by experts (including psychiatrists, psychopharmacologists, and
28
29 consumer consultants) and will include the following topics:
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33 1. *Complex issues relating to psychotropic medication (adherence and side effects).* This module
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35 will discuss the role of psychotropic medications, including an exploration of the barriers and
36
37 enablers to adherence, and the consequences of poor adherence. It will also discuss complex
38
39 issues relating to psychotropic medication use, such as weight gain and diabetes.
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43 2. *Physical health issues for people living with SPMI.* This module will explore the evidence
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45 regarding the importance of physical health care and exercise for people living with SPMI. It
46
47 will also include information on active lifestyles, cardiometabolic risk, tobacco use and
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49 resources.
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53 3. *Evidence-based strategies to improve medication adherence and physical health care.* This
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55 module will equip pharmacists with evidence-based strategies including guidance on
56
57 addressing cardiovascular risk factors, and sensitive issues such as weight management,
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59 smoking cessation, dental health, and medication adherence.
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3 4. *Communication, motivational interviewing and goal setting.* This module will help pharmacists
4 develop appropriate and person-centred communication skills and strategies to work with
5 participants to set, and reach, their mental and physical health goals.
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10 Case studies and role-play activities will be integrated throughout the modules to provide IG
11 pharmacists with opportunities to practice and apply their newly acquired skills, including the use
12 of research tools and questionnaires. Prior to the first workshop commencing specific aspects of the
13 training will be video-recorded to consistency in delivering the intervention to all workshops. The
14 training modules will be made available online for IG pharmacists to access as needed for reference
15 purposes.
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24 The continued wellbeing of participants living with SPMI is a key aspect of the training.
25 Information on mental health and crisis support numbers and websites will be part of the resources
26 provided, e.g. Lifeline, BeyondBlue. Furthermore, communication between pharmacists and the
27 participant's treating team will be ongoing throughout the RCT, thus helping to ensure that any
28 deterioration in health status, or concerns about wellbeing, will be immediately recognised and
29 addressed.
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38 Recruited community pharmacies will be required to send at least two pharmacists (one of
39 whom can be an intern pharmacist^o working under the supervision of a registered pharmacist) to
40 complete the *PharMIbridge* training components. All pharmacies will be encouraged to invite
41 additional pharmacy support staff to complete and attend the B-MHFAP component and
42 information session on research processes, to support pharmacists in delivering the intervention/
43 comparator and establish 'Mental Health Friendly Pharmacies'. Ultimately, trained registered
44 pharmacists will take responsibility for delivering the *PharMIbridge* intervention. For example,
45 while only the pharmacist can be involved in addressing MRPs, a pharmacy support staff member
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3 with well-established consumer relationships could assist with promotion, be involved with
4 identifying eligible participants, making follow-up appointments, or sending reminders.
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8 A pilot workshop of the non-B-MHFAP training components will involve a convenience
9 sample of pharmacy students, intern and registered pharmacists, and all RCT trainers/mentors.
10
11 Feedback will be sought through pre- and post-training questionnaires and focus group discussions
12 at the conclusion of pilot training. This feedback will help identify whether modifications to the
13 training are required prior to its delivery as part of the RCT.
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21 **Training mentors**

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23 The IG training components will be delivered by a local pharmacist and consumer mentor
24 partnership in each RCT region who will also provide ongoing support for IG pharmacy staff
25 throughout the RCT. The combination of a pharmacist educator with experience in community
26 pharmacy practice and a consumer educator with lived experience of mental illness working as a
27 mentor pair has been shown to facilitate implementation of a mental health support service for
28 consumers with depression and anxiety.⁴⁶ The mentor pair will personally visit the IG pharmacies
29 in their RCT region on a minimum of two occasions during the intervention period. In addition to
30 these visits, mentors will provide regular support through phone calls, emails and other modalities,
31 as required. Moreover, the training team will provide two refresher webinars in each RCT region;
32 these will be led by the two mentors. Webinars will focus on problem-solving discussions and co-
33 learning perhaps using examples of ‘what has worked well’/‘not so well’ to stimulate conversation.
34 Refresher content will be based on two additional, pre-recorded, case-scenarios allowing
35 pharmacists to revise the skills they have been applying in practice.
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56 **Study outcomes**

57 **Primary outcome**

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3 The primary outcome is the difference in medication adherence rates between the IG and CG at
4 RCT conclusion (six-months). Medication adherence will be identified using both routinely
5 collected data (pharmacy dispensing and PBS) and self-reported measurements of adherence; the
6 Reported Adherence to Medicine (RAM)⁵² scale which has been validated for use among people
7 with psychosis, schizoaffective disorder and schizophrenia.⁵³ PBS and pharmacy dispensing data
8 will be used to confirm self-reported data by calculating: i) the Medicine Possession Ratio (MPR),
9 which refers to the proportion of days that a consumer is in possession of their medicine within a
10 defined period; and ii) Medicine Persistence, which refers to a specified time-period when there has
11 been a delay in medicine re-fill.⁵⁴ A pilot of the selected tools will be undertaken in the set-up stage
12 of the *PharMIbridge* RCT (Figure 1 and Table 1) to ensure that they are practical, valid and feasible
13 to use within the RCT time-frame.
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31 Secondary outcomes

32 *Health outcomes*

33 Clinical measures including weight, body mass index, abdominal girth and blood pressure,⁵⁵ will
34 be collected at two time-points; when participants complete the baseline and 6-month follow-up
35 questionnaires. Pharmacists will collect these measures in the pharmacy and/or from patient/health
36 care records. Additionally, participants will be asked (at baseline and 6-month follow-up) if, in the
37 last 12 months, they have had a risk assessment for cardiovascular disease and a glycated
38 haemoglobin (HbA1c) blood test to assess for diabetes. Participants physical health will be
39 evaluated using self-reported questionnaires, including the Physical Activity "Vital Sign" (PAVS)
40 Questionnaire⁵⁶ and selected questions from the Australian Health Survey on Dietary Behaviour.⁵⁷
41 The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) will also be used to
42 screen for substance use.^{58 59}
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3 Additional tools such as the My Medicines and Me Questionnaire (M3Q)⁶⁰ exploring
4 psychotropic medication side-effects; the Simple Physical Activity Questionnaire (SIMPAQ)^{61 62}
5 which identifies time spent on physical activity; the Pittsburgh Sleep Quality Index (PSQI)⁶³
6 exploring sleep quality, the Fagerström Test for Nicotine Dependence⁶⁴ and the Brief Pain Inventory
7 (BPI)⁶⁵ identifying pain-related concerns, will assist IG pharmacists with intervention delivery.^{65 66}
8 This combined information will inform the development of goals for IG consumer participants, with
9 goal achievement reviewed at each follow-up, and at the final six-month, consultation using the
10 Goal Attainment Scale (GAS).⁶⁷
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21 *Quality of life, medication experiences and illness beliefs*

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23 Difference in self-reported quality of life (e.g. Assessment of Quality of Life, AQoL-6D),⁶⁸
24 psychological wellbeing (Kessler Psychological Distress Scale, K-6), sleep problems (Insomnia
25 Severity Index, ISI),⁶⁹ medication burden (Multimorbidity Treatment Burden Questionnaire,
26 MTBQ),⁷⁰ attitudes (Drug Attitude Inventory 10, DAI-10),^{71 72} illness beliefs (Brief Illness
27 Perception Questionnaire, BIPQ),⁷³ and health care service utilisation (e.g. frequency of GP follow-
28 up or referrals, pharmacist action/s, hospitalisation(s) and emergency department admissions) will
29 be measured between and within RCT arms at baseline and at 6-months. An evaluation of the
30 identification and number and type of MRPs (including side-effects), and adherence to other
31 prescribed medication, will be undertaken at baseline and six-month follow-up.
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44 It is anticipated that the *PharMIbridge* intervention will further optimise health care utilisation
45 by increasing pharmacist communication and collaboration with other health practitioners and other
46 support people involved in the participant's care. The RCT will involve increased use of
47 MedsChecks by community pharmacists for this vulnerable population. Difference in Federal
48 Government healthcare resource use (measured as the total of primary health care services,
49 laboratory tests and medications; and MBS data) will be sought from the Australian Government
50 Department of Human Services, with participant consent.
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Pharmacy staff evaluation of training

Evaluation of the B-MHFAP training will be undertaken as a standard component of this accredited course.⁷⁴ An evaluation of the *PharMIbridge* training programme in terms of its effectiveness (in comparison to B-MHFA alone) to reduce stigma and build the required skills for pharmacists to work with people living with SPMI will involve pre- and post-training questionnaires, which will be repeated at RCT conclusion. The questionnaires will collect both qualitative and quantitative data including items adapted from validated scales such as the Social Distance Scale,⁷⁵ the Mental Illness Attitude Questionnaire,⁷⁶ and the Metabolic-Barriers, Attitudes, Confidence, and Knowledge Questionnaire (M-BACK).⁷⁷ Additional questions will specifically focus on pharmacist confidence in providing MHFA,⁴⁴ willingness to provide services for mental health consumers^{14 78 79} and barriers and incentives to working with people living with SPMI.⁶

PharMIbridge service evaluation

A proportion of IG consumer participants and pharmacists will be invited to participate in a telephone interview at RCT conclusion to qualitatively explore the acceptability and impact of the *PharMIbridge* intervention. Up to five consumer participants from each RCT region will be invited for interviews (max=20) as well as one pharmacist from each pharmacy who participated in the RCT (max=24). The participant interview guide will explore topics including: i) medication adherence and current medications; ii) types of MRPs experienced and resolved; iii) health literacy in relation to psychotropic medicines; iv) changes in relationship between participants, pharmacists and other health care professionals; and, iv) satisfaction with the *PharMIbridge* intervention. An additional participant-reported experience measure will be developed and included at the end of the service delivery in the Final Health Review. A short online survey will also be developed to explore service acceptability for other health practitioners who interact with the intervention, and other pharmacy staff, e.g. pharmacy assistants.

Data collection

The RCT data collection tools and processes will be piloted prior to use (Figure 1). Data will be collected from consumer participants, pharmacy staff and other health care professionals (Table 1).

Consumer participants will be required to consent to their MBS, PBS, hospitalisation and emergency department data being accessed by researchers for a period of 12-months prior to, and six-months after, enrolment in the RCT. The reason for collecting data about resource use up to 12-months prior to the RCT is to test for baseline differences which can then be adjusted for during analysis.

Participant data collected by pharmacists will be entered directly into purpose-built IG and CG research modules within GuildCare NG™. This cloud-based pharmacy software platform is used by the majority of community pharmacies in Australia for the delivery of professional service programs such as MedsCheck; it also links to dispensing systems. In the IG, nominated members of the participant's treating team (i.e. GP, psychiatrist, mental health case manager) will be provided with access to their individual consumer participant's research records to facilitate timely access to, and exchange of, shared information.

Participating community pharmacies will receive funding to support their research involvement, including an administration fee for training attendance, research administration and data management (ranging from \$3,700-\$10,712 depending on urban/rural/remote location), as well as a per-participant fee for initial and follow-up consultations, and for six-month data collection. IG pharmacies will be remunerated for the baseline data collection and Initial Health Review (75 minutes; \$167), follow-up consultations (Level 1: up to three consultations; \$66, or Level 2: greater than three consultations; \$133), and for the Final Health Review and follow-up data collection (30 minutes; \$167). Service fees for CG pharmacists include the MedsCheck consultation and baseline data collection (60 minutes; \$133) and the six-month follow-up data collection (30 mins; \$66). A

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3 gift voucher valued at AUD\$30 will be offered to all consumer participants at the final, six-month
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5 data collection point in recognition of their time for completing data collection processes that would
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7 not normally be part of their health care.
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10 11 12 **Sample size** 13

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15 Based on a recent study conducted in a similar population,⁶ we assume the baseline rate of non-
16
17 adherence assessed using pharmacy dispensing data will be 56%. This outcome will be available
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19 for all participants (unless actively withdrawn), regardless of treatment adherence. We assume the
20
21 percentage of non-adherent participants in the CG arm will drop to 51% (based on the results of
22
23 previous studies exploring adherence as an outcome of a MedsCheck service),³⁰⁻³³ and the
24
25 percentage of non-adherent participants in the IG arm will drop to 35%.⁶ With $\alpha=0.05$, the RCT
26
27 will have 80% power to find a statistically significant difference between RCT arms with 149
28
29 individuals recruited to each arm (without accounting for clustering).
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33 As this is a cluster-RCT we need to account for the non-independence of observations from
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35 individual participants recruited from the same pharmacy. We assume a median number of 10
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37 participants at each pharmacy, and conservatively assume the $ICC=0.03$, giving a design effect of
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39 1.27. Consequently, a total of 190 participants will need to be recruited in each arm (380 in total).
40
41 To achieve this, 10 consumer participants will need to be enrolled from each of 38 pharmacies.
42
43 Assuming that 20% of pharmacies will withdraw from the RCT without enrolling any participants,
44
45 a total of 48 pharmacies will need to be recruited.
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50 51 **Data analyses** 52

53
54 Descriptive statistics will be used; mean (standard deviation) or median (25th-75th percentile) for
55
56 continuous data and frequency (percentage) for categorical data. We will compare the primary
57
58 outcome of percentage adherence between RCT arms using a mixed-effects logistic regression
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3 model, with treatment arm entered as the fixed effect and pharmacy entered as a random effect, to
4
5 account for possible non-independence of observations from participants who attend the same
6
7 pharmacy. Results will be reported as odds ratios and 95% Wald-based confidence intervals.
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10 For secondary analyses, interval data will be analysed using mixed-effects linear regression,
11
12 binary data using mixed-effects logistic regression, and count data using mixed-effects Poisson
13
14 regression models. In all cases, the likely non-independence of data from individuals enrolled
15
16 through the same pharmacy will be accounted for as random effects in the regression models.
17
18 Analyses will be based on the intention-to-treat principle, with participants analysed according to
19
20 the treatment they were allocated to receive. Data will be analysed using Stata statistical software
21
22 (StataCorp, College Station, TX, USA), with significance set at less than 0.05.
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26 Qualitative interviews will be audio-recorded (with participant consent), transcribed verbatim
27
28 and quality checked. Thematic analysis will be conducted by experienced qualitative researchers
29
30 within the research team. This process involves reading and re-reading transcripts to identify,
31
32 analyse and report patterns within the data, leading to the identification of similar codes across the
33
34 entire data set.⁸⁰ Initial codes are thereby sorted into themes and subthemes.⁸⁰
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40 **Economic evaluation**

41
42 We hypothesise that the provision of the *PharMIbridge* intervention will be cost-effective compared
43
44 to standard care from a health care sector perspective with regard to RCT-based costs and outcomes
45
46 (cost per additional participant adherent/cost per [proxy] health outcome). The base case analysis
47
48 will comprise the cost per additional 'adherent' participant for the IG compared with the CG and
49
50 reported as the incremental cost-effectiveness ratio (ICER). The outcome for the base case analysis
51
52 is the difference in the change in the proportion of 'adherent' participants from baseline to RCT
53
54 conclusion, between the IG and CG. Sub-group analyses will be conducted for the primary outcome
55
56 measure (adherence) based on participant characteristics. Regression analyses using 'adherence' as
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3 the dependent variable will be performed to assess if the effect of the intervention varies by SPMI
4
5 diagnosis, age, gender, pharmacy location and number of other medications taken concurrently.
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7 Any evidence of non-linearity will be adjusted for using appropriate transformations.
8
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10 A cost per Quality Adjusted Life Year (QALY) gain will also be conducted based on health-
11
12 related Quality of Life data collected within the trial. QALYs will be estimated by applying
13
14 Australian utility weights and using the area under the curve approach. Difference in QALYs
15
16 between the IG and CG will be estimated using linear or non-linear regression methods depending
17
18 on the nature of the data. The analytical time-frame for the cost effectiveness analyses will be
19
20 limited to that of the follow-up period of the trial. This is the most conservative approach relative
21
22 to translation of the primary outcome measure, adherence, where there is likely to be heterogeneity
23
24 of medications and conditions.
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28 Costs will be considered from the health system perspective and include both the cost of
29
30 interventions and the cost consequences from potential changes in health care utilisation. The
31
32 difference in health resource use for all participants will be collected and analysed based on
33
34 administratively collected MBS, PBS and pharmacy dispensing data.
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40 Included costs

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42 The difference in health resource use for all participants will be collected and analysed from their
43
44 MBS and PBS records six-months prior to, and during, enrolment in the RCT. Impact of seasonality
45
46 will also be assessed for the same 12-month period. The economic evaluation will quantify costs
47
48 associated with the *PharMIbridge* intervention at a participant level in the eligible population. The
49
50 costs measured in the economic evaluation should be equivalent to their ‘opportunity cost’, i.e.
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52 assessed in terms of the monetary value of the benefits that are foregone because the resources are
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54 not available for their best alternative use. The opportunity cost will be estimated from the market
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56 costs of the resources consumed, whenever available. Costs from the RCT include, but will not be
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3 limited to: i) the training of pharmacists to provide the *PharMIbridge* intervention; ii) the fee-for-
4 service to pharmacists; and, iii) the clinical software adaption to facilitate the identification of ‘non-
5 adherent’ participants and record interventions.
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10 11 12 Cost data analysis 13

14 The source of any variation (if observed) in costs between intervention and comparator arms, as
15 well as the cost ‘drivers’, will be investigated with a Generalised Linear Model (GLM) using a
16 standard statistical software package (STATA). As cost data are not likely to be normally
17 distributed, a gamma log-link function or similar will be used, with appropriate testing of the GLM
18 specification using the modified Park test and link test. Full costing will be provided for the RCT.
19 If certain costs are not included in the economic evaluation, any assumptions, and the effect of their
20 exclusion, will be specified in the analysis.
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30 Costing of the *PharMIbridge* intervention will be undertaken as follows: i) identify
31 administrative resources used in program management, with RCT-specific administrative resources
32 separated from activities that would be included in a national roll-out of the program; ii) some
33 resource use will be measured in natural units (for example, clinical staff time spent on delivering
34 the *PharMIbridge* intervention) and will be valued in monetary units; iii) other resources can be
35 directly valued (for example, incentive payments to staff and services); and, iv) if the *PharMIbridge*
36 intervention delivery requires additional equipment (e.g. privacy screen), market costs will be
37 estimated with amortisation applied over the useful life of the equipment.
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51 Sensitivity analysis 52

53 The uncertainty in effect sizes and costs will translate into a degree of uncertainty around the
54 estimated ICER. This uncertainty will be explored using a system of seemingly unrelated regression
55 equations. This has been chosen because it has been argued that such methods are generally robust
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3 to skewed data, and to allow for any correlation between costs and effects. The cost and adherence
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5 (or QALY) regressions will be run simultaneously, including SPMI diagnosis, age, gender,
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7 pharmacy location and number of other medications taken concurrently included (as covariates) to
8
9 explore potential sub-group differences with respect to adherence, costs or cost-effectiveness.
10
11 Additionally, in order to estimate the level of uncertainty associated with the decision as to whether
12
13 or not the intervention was cost-effective, we will use the non-parametric bootstrap technique (with
14
15 5,000 replications sampled with replacement) to estimate the probability that the intervention is
16
17 cost-effective over a range of willingness to pay per outcome (adherer / QALY) according to the
18
19 cost-effectiveness acceptability curve.
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26 Financial appraisal

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28 Financial appraisal and full pathway costing will be undertaken as part of the *PharMIbridge* RCT.
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30 Where assumptions for identification, measurement and valuation of economic costs differ to
31
32 financial costs, these differences will be specified. The cost to the health sector if the *PharMIbridge*
33
34 intervention was implemented nationally will be extrapolated over a five-year time frame.
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40 Patient and public involvement

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42 To provide maximum benefit to people with SPMI, health services need to be relevant, accessible
43
44 and responsive to their needs. The views of people with lived experience of a mental illness will be
45
46 paramount to the success of the *PharMIbridge* RCT, from their involvement in the development of
47
48 the RCT protocol as members of the research team, development and implementation of the
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50 intervention with pharmacy staff as trainers and mentors, and as representatives on the Expert Panel
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52 who will have oversight across the lifetime of the research. A working group of partner organisation
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54 representatives, consumer representatives, and experts actively involved in improving mental health
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3 care will co-develop training material. People with lived experience of SPMI will also inform
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5 dissemination strategies based on the RCT findings.
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10 DISCUSSION

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12 The *PharMIbridge* RCT will use the medication expertise of community pharmacists to support
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14 medication adherence and address the physical and mental health needs of participants using
15
16 psychotropic medication for SPMI. The focus on the physical health of people living with SPMI is
17
18 of utmost importance given the considerable life expectancy gap attributable to physical
19
20 comorbidities in this population. Beyond improved consumer participant wellbeing, the
21
22 *PharMIbridge* RCT is expected to facilitate better relationships between pharmacists and local
23
24 health services, including community mental health teams, PHNs and GPs. Lastly, by providing a
25
26 diverse range of mental health services and resources and by increasing community outreach to
27
28 mental health and non-mental health related services IG pharmacies will become more prominent
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30 in the mental health sector
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35 Although the provision of a MedsCheck service for people using high-risk medication such as
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37 psychotropics (in addition to other criteria), is a currently funded service, there is evidence that
38
39 pharmacists' mental health literacy concerning SPMI is lower in comparison to other mental
40
41 illnesses.⁴⁰ Most people using antipsychotics and/or mood stabilisers would be eligible for a
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43 MedsCheck, however, we believe that this vulnerable population may be missing out on this service
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45 as it is not specifically targeted towards mental health consumers. Therefore, the proposed
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47 *PharMIbridge* intervention is a novel service within the community pharmacy setting and is, to our
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49 knowledge, the first RCT to determine the impact of a pharmacist-led support service for people
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51 living with SPMI.
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56 All pharmacy staff involved in the RCT will receive B-MHFA. Hence, the *PharMIbridge* RCT
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58 provides an opportunity for all consumer participants to access a recognised standard level of care.
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3 Furthermore, analyses conducted on the CG consumer participant outcomes will allow us to identify
4 the impact of MedsCheck for consumers living with SPMI. This is particularly important given the
5 current lack of data regarding the impact of MedsChecks on medication adherence. Furthermore, it
6 is unrealistic and unethical to expect that consumer participants living with SPMI and enrolled into
7 the CG receive no form of care or service. These participants will be asked to complete a range of
8 surveys at baseline which are likely to identify adherence and health issues, and consequently
9 pharmacists would be expected, as health care professionals, to intervene in such situations. Thus,
10 the research team also anticipates positive outcomes for CG participants, although this effect is
11 hypothesised to be inferior to IG participants.
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24 There are some limitations to this RCT. While a key focus of this research is the physical health
25 care needs of consumer participants, the follow-up time of six-months is insufficient to use physical
26 health as a primary outcome measure. The RCT duration was selected to meet the specified time-
27 frame requirements of the funding body. Hence, the long-term impact of the *PharMIbridge*
28 intervention cannot be determined. It should be noted that the RCT sites, while specifically chosen
29 to reflect a variety of geographical regions, types of pharmacies, mental health services and socio-
30 economic factors, may not be generalisable to the Australian population. Lastly, as adherence is
31 known to be an inherently difficult concept to measure, to ensure accurate and comprehensive
32 assessment the research team will use multiple objective and subjective measures to assess this
33 outcome. Notwithstanding these limitations, the *PharMIbridge* RCT will provide valuable insights
34 into the future implementation of a community pharmacy-based, mental health support service
35 across Australia.
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54 **Ethics and dissemination**

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56 This RCT protocol and training program has been approved by Griffith University Human Research
57 Ethics Committee (2019/473 and 2019/493). The trial has been registered with the Australia and
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3 New Zealand Clinical Trials Registry (ANZCTR12620000577910). At the conclusion of the
4 *PharMIbridge* RCT, a report will be submitted to the Australian Government Department of Health
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6 and partner organisations. A dissemination plan will be developed by the research team, project
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8 partners and the Expert Panel. A summary of findings for all participating pharmacies and consumer
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10 participants will be provided at the end of the RCT. Results will be published as manuscripts in
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12 peer-reviewed journals and presented at national and international scholarly conferences and
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14 symposia.
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24
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26
27 Sydney. We thank Dr Helen Stapleton for her feedback on the manuscript.
28
29

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31
32 investigators on the funding proposal. AW and COR are co-principal investigators and led the
33
34 intervention and training development and evaluation plan. JB provided expert oversight of the
35
36 economic evaluation plan, assisted with the selection of primary outcome measures and datasets.
37
38 SM and SE-D led the ethics application process, review of data collection tools and contributed to
39
40 the intervention and training development and evaluation plan. RW provided statistical expertise
41
42 and sample size calculations for the RCT. All authors were involved in the revision of this protocol
43
44 and made a significant contribution towards its intellectual content and approved the final version
45
46 of the manuscript.
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50
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3 **Competing interests** None declared.
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6 **Patient Consent** Not required.
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9 **Ethics approval** Griffith University Human Research Ethics Committee (HREC/2019/473 and
10
11 HREC/2019/493).
12

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14 **Provenance and peer review** Not commissioned; peer reviewed for ethical and funding approval
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16 prior to submission.
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26 **Figure 1:** Overview of the research stages and timing

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28 **Figure 2:** Overview of the *PharMIbridge* RCT
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Table 1: Data collection

Type of evaluation	Description/measure	Data source	Time-point in weeks (RCT)		
			Before RCT	0	26
Formative	Training evaluation (paired pre- and post-questionnaires)	Pharmacists in IG and CG			
Adherence	MPR and medicine persistence RAM ⁵² scale	Pharmacy			
		PBS data			
		GuildCare NG TM documentation (all consumer participants)			
Medication outcomes	Identification of MRPs and management (MedsCheck or DOCUMENT system ⁸¹)	GuildCare NG TM documentation (all consumer participants)			
Goal achievement	Type and number of goals set, goal achievement (GAS) ⁶⁷	GuildCare NG documentation (IG consumer participants)			
Clinical measurements	Clinical measures for each consumer participant - Weight / Height (Body Mass Index) - Abdominal girth - Blood pressure	GuildCare NG TM documentation (all consumer participants)			
		Prescribers / other health workers			
Health and related outcomes	- PAVS, ⁵⁶ Dietary Behaviour, ⁵⁷ ASSIST ^{58,59} AqoL-6D, ⁶⁸ ISI, ⁶⁹ MTBQ, ⁷⁰ DAI-10, ^{71,72} BIPQ, ⁷³ K6 ⁸² - M3Q ⁶⁰ SIMPAQ, ^{61,62} PSQI, ⁶³ Fagerström Test for Nicotine Dependence, ⁶⁴ BPI ^{65,66}	- GuildCare NG TM documentation (all consumer participants)			
		- IG consumer participants only			
Impact	- Consumer reported experience measure - Semi-structured interviews (service implementation, acceptability) - Online survey (service acceptability)	- IG consumer participants only			
		- IG consumer participants (n=20), IG pharmacists (n=24) - Other health care professionals (e.g. GP, psychiatrist, MH case manager) and IG pharmacy staff			
	Health care utilisation	Primary care, MBS, hospitalisation			
Economic appraisal	RCT-based economic evaluation (e.g. resources, incentive payments, time) Cost-effectiveness (health-care sector perspective)	Cost of intervention, MBS, PBS, pharmacy dispensing data			
		AQoL-6D ⁶⁸			
		Cost per additional adherer Cost per additional quality adjusted life year			

Hospitalisation, Emergency department admissions, MBS and PBS data will be obtained for 12-months before, and the entire duration of the RCT. Health outcomes data and prescription dispensing data will be obtained for the entire length of the RCT. Abbreviations: ASSIST=Alcohol Smoking and Substance Involvement Screening Test; AqoL-6D=Assessment of Quality of Life; BIPQ = Brief Illness Perception Questionnaire; DAI-10 = Drug Attitude Inventory 10; DOCUMENT=Drug selection, Over/Under dose, Compliance, Untreated indications, Monitoring, Education or information, Non-clinical, Toxicity or adverse reactions; GAS=Goal Attainment Scale; ISI=Insomnia Severity Index; K6=Kessler Psychological Distress Scale; M3Q=My Medicines and Me Questionnaire; MPR=Medicine Possession Ratio; MTBQ=Multimorbidity Treatment Burden Questionnaire; PAVS=Physical Activity Vital Sign Questionnaire; BPI=Brief Pain Inventory; PSQI=Pittsburgh Sleep Quality Index; RAM=Reported Adherence to Medicine Scale; SIMPAQ=Simple Physical Activity Questionnaire.

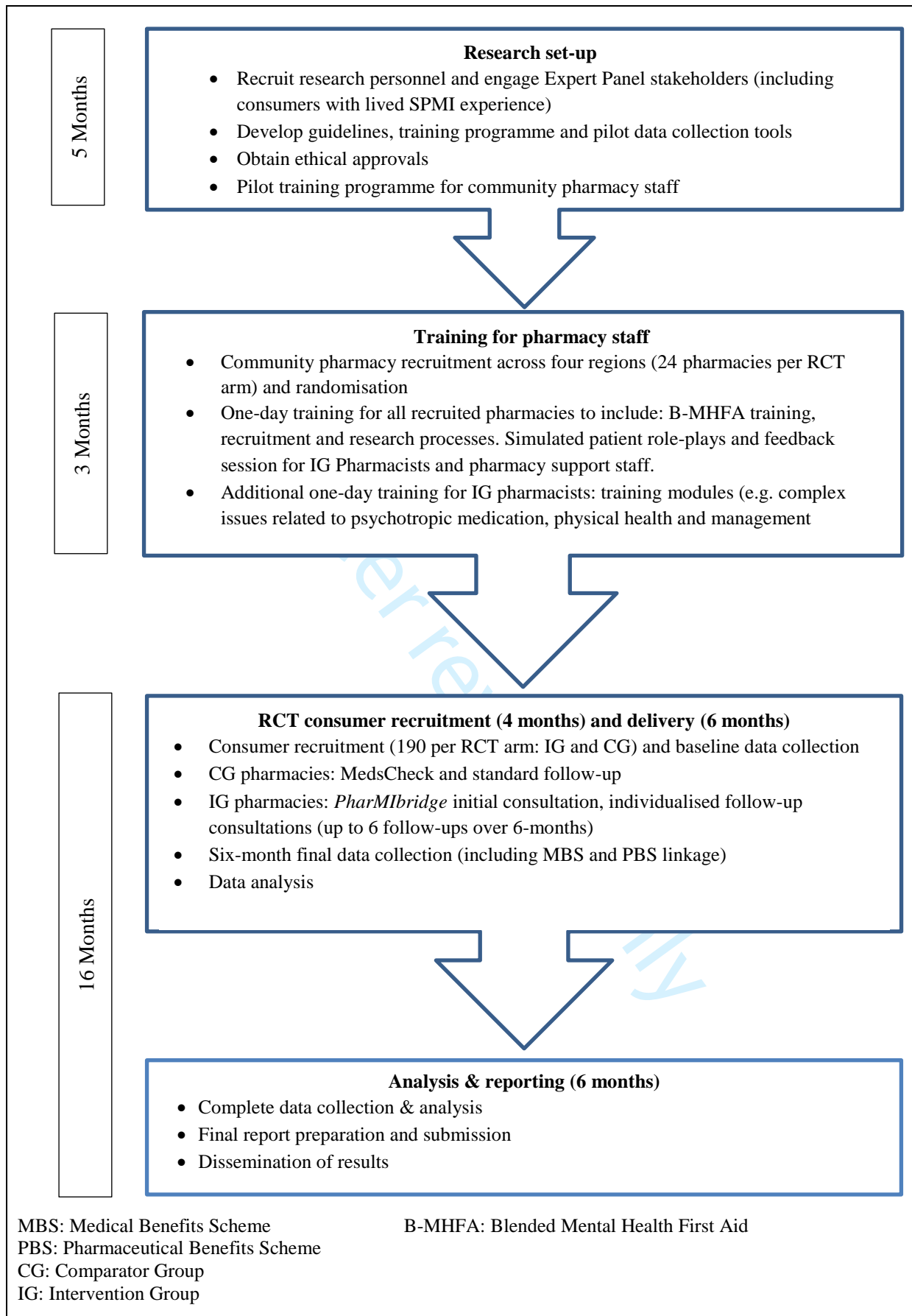


Figure 1: Overview of the research stages and timing

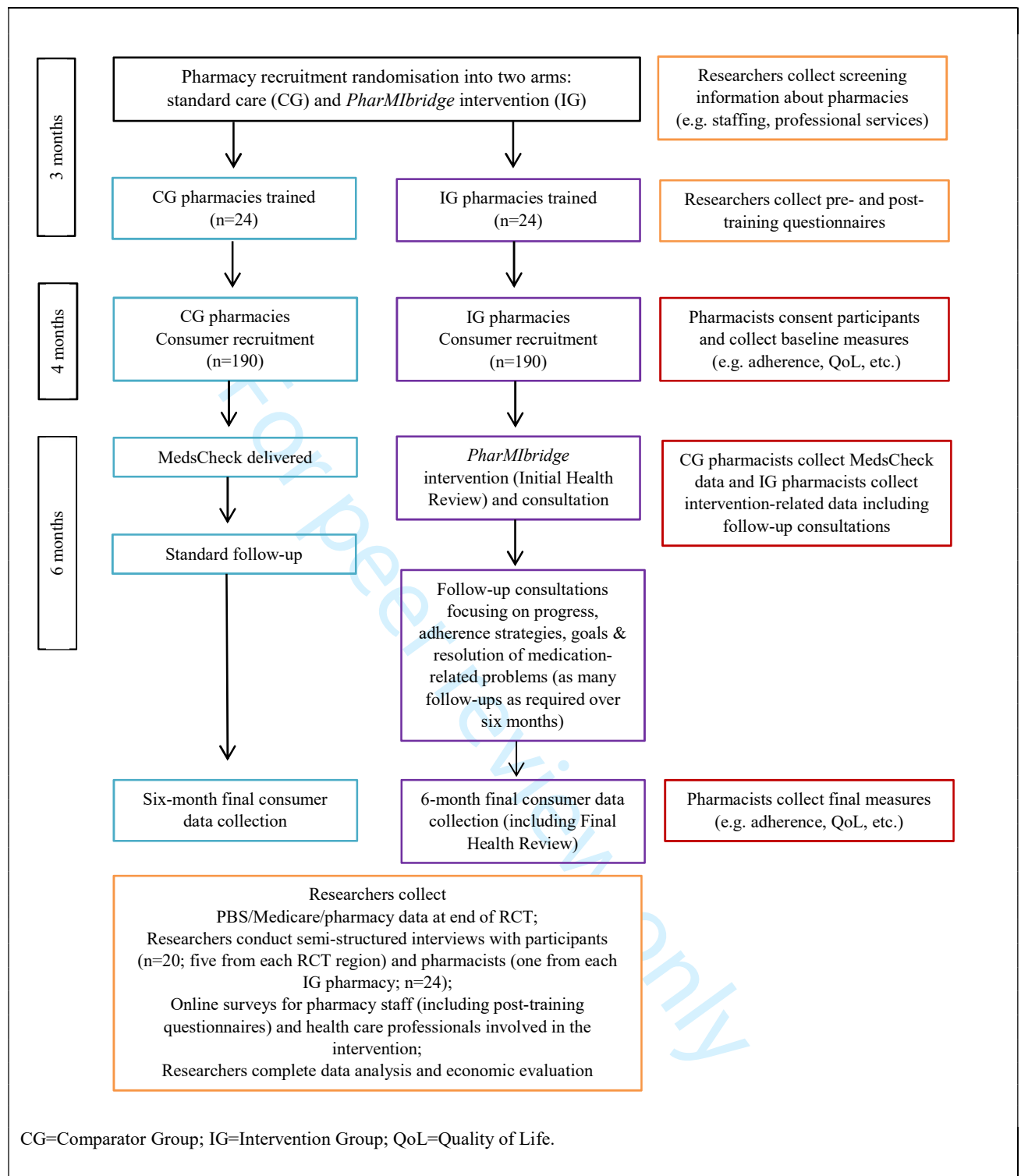


Figure 2: Overview of the *PharMIbridge* RCT



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Pages in Protocol
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Pg.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Pg.28
	2b	All items from the World Health Organization Trial Registration Data Set	Pg.1, 2, 6, 8-12, 17-22, 28, 29 N/A: completion date, summary results.
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	Pg.29
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Pg. 1, 29.
	5b	Name and contact information for the trial sponsor	Pg. 29 This information is reported in the Clinical Trial Registration ANZCTR12620000577910
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Pg.29
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Pg.8

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Pg.5-6
	6b	Explanation for choice of comparators	Pg.6-7. This information is reported in the Clinical Trial Registration.
Objectives	7	Specific objectives or hypotheses	Pg.6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory).	Pg.1, 7, 22.
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Pg.8-9.
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Pg.9-11.
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pg.11-16.
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g. drug dose change in response to harms, participant request, or improving/worsening disease)	N/A as the intervention will be tailored to each individual participant (see Pg. 11 and 13)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g. drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Pg.17-20,
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Pg.11-13. See Figure 2. This information is also reported in the Clinical Trial Registration.
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Pg.21-22.
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Pg.8, 10, 16.
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Pg.9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	This information is reported in the Clinical Trial Registration.
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	This information is reported in the Clinical Trial Registration.
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A This information is reported in the Clinical Trial Registration.
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A This information is reported in the Clinical Trial Registration.

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Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Pg. 17-21, 39
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Pg.21 This information is reported in the Clinical Trial Registration.
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Details of the data management processes are outlined in our Ethics application which is approved.
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Pg.22-23.
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Pg.24-25.
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	This information is reported in the Clinical Trial Registration.
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	This information is reported in the Clinical Trial Registration.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Pg.16-17 This information is reported in the Clinical Trial Registration and ethics application (approved)

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Pg. 29.
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	This information is reported in the Clinical Trial Registration.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Pg. 14 This information is reported in the Clinical Trial Registration.
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Pg. 12, 20.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Details of our data management processes are outlined in the Ethics application (approved) as well as consumer information and consent forms.
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Pg.29.
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	This information is reported in the Clinical Trial Registration.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Details regarding the action/s to take if there is any participant harm are outlined in the Ethics application (approved) as well as consumer information and consent forms.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Pg.28.

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	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A as ICMJE recommendations will be followed.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	This information is reported in the Clinical Trial Registration.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Informed consent materials were provided in the Ethics application (approved).
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

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