

**A CLUSTER RANDOMISED CONTROLLED
TRIAL OF A MEDICINEINSIGHT
EDUCATIONAL QUALITY IMPROVEMENT
PROGRAM TO IMPROVE THE DIAGNOSIS
AND TREATMENT OF CHRONIC HEPATITIS C
IN GENERAL PRACTICE**

- THE EQUIP-HEPC TRIAL

Protocol and project information

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Independent, not-for-profit and evidence based, NPS enables better decisions about medicines and medical tests. We are funded by the Australian Government Department of Health.



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1. BACKGROUND

Chronic hepatitis C (CHC) in Australia

Chronic hepatitis C (CHC) is a major public health threat, comparable to HIV and malaria¹. It's estimated that 182,283 people in Australia were living with the condition at the end of 2017 and at risk of developing long term liver disease². People with CHC are at risk of progressive liver fibrosis leading to cirrhosis, liver failure and hepatocellular carcinoma (HCC). Until recently, only 20% of people living with chronic hepatitis C infection ever received treatment, which had limited effectiveness and poor tolerability.³ However, new orally administered direct acting antiviral (DAA) treatments have shown cure rates of over 95%, are largely well tolerated and have been reimbursed on the Australian Pharmaceutical Benefit Scheme (PBS) since 1 March 2016. The majority of people in Australia can potentially be cured of hepatitis C, reducing their chance of getting liver disease and other serious complications.

CHC was previously a condition primarily managed by specialists. However, the listing of DAA regimens on PBS, expanded prescriber eligibility and the release of Australian recommendations for the management of CHC in 2016 have expanded the role of general practitioners (GPs) in the management of patients with CHC. The shift to primary care of uncomplicated non-cirrhotic CHC aims to improve overall treatment access and uptake.² With the new oral interferon-free treatments and new models of care we have the potential to revolutionise hepatitis C treatment in Australia.

Australia has committed to the WHO CHC goals including 90% diagnosed, 80% treated, and 65% reduction in mortality by 2030.¹ This will only happen in Australia with continued treatment momentum which arguably needs to be led in primary care. There is a need for targeted interventions to normalise treatment of CHC in primary care.⁴

In addition to improving the uptake of hepatitis C treatment overall, targeting populations with high hepatitis C virus transmission risk could fast track CHC elimination by preventing new infections. Around 80% of people living with CHC contracted the infection through sharing unsterile injecting equipment and almost every new infection occurs in people who inject drugs (PWID). There is clear evidence of equivalent treatment outcomes and potential to reduce transmission.³

Primary care management of CHC

The shift in 2016 to management of CHC in primary care has begun to remove barriers to people accessing treatment. Large numbers of Australians have already been cured using DAA regimens, however, the numbers presenting for treatment have begun to plateau.⁵ Between March 2016 and March 2018, 58,280 patients started DAA treatment, equating to 26% of the people living with CHC in Australia.² However, treatment initiation rates have more than halved, from 3000–5000 patients per month in the first six months following PBS listing to <1500 per month January-March 2018.²

It is estimated that 74% of people living with CHC in Australia remain untreated. Primary care providers play a key role in re-engaging those diagnosed with CHC some years ago who should now be considered for DAA treatment, and in detecting the 25% of people with CHC who are unaware of their infection.⁶

Guidelines released by the Gastroenterological Society of Australia (GESA) and its specialty sub-group the Australian Liver Association (ALA) have a particular focus on up-skilling and supporting primary care providers in the identification, treatment and management of CHC.⁷ Overall, 52% of individuals have been prescribed DAA treatment by specialists and 27% by GPs. The proportion of individuals prescribed DAA treatment by GPs increased from 8% in March 2016 to 38% in the first three months of 2018².

Australian qualitative research conducted one year after the PBS listing of DAA therapies with key stakeholders from primary care, government and non-government sectors warned the momentum was waning and that targeted interventions to normalise CHC treatment within primary care were needed. They recommend workforce training and resources for clinicians should be prioritised as many have limited CHC experience. Additional systematic activity was also advised to ensure that the DAA-access momentum is maintained and CHC elimination achieved.⁴

Evidence based interventions to improve CHC management in primary care

Evidence-based interventions to improve CHC assessment, treatment, and adherence generally fall into one of 4 categories, including those involving: 1) diagnosis or case-finding; 2) linkage to HCV care; 3) pre-therapeutic evaluation or treatment initiation; or 4) treatment adherence.⁸ Below we describe interventions focused on 1) and 3) targeted to primary care in the DAA era as most relevant to this study.

Few studies have assessed interventions designed to improve the identification and management of patients with CHC in primary care. We await results of two ongoing studies in primary care, the first being the Hepatitis C- Assessment to treatment (HepCATT) cluster randomised controlled trial (cRCT).⁹ This RCT will be evaluating the effectiveness of a complex intervention in general practices in South West England to improve diagnosis and evaluation for treatment. The intervention involves: educational training on CHC for the practice; poster and leaflet display in the practice waiting rooms to raise awareness and encourage opportunistic testing; and a CHC risk prediction algorithm based on information on possible risk markers in the electronic patient record using an audit tool. The audit will then be used to recall and offer patients an HCV test. The primary outcome is the number and rates of HCV testing, with results yet to be published.⁹

The second ongoing study is the non-randomised HepLink pilot study in Europe including 24 Opioid substitution therapy (OST) general practices recruited to assess the effectiveness of an integrated model of care comprising education of community practitioners, outreach of an CHC-trained nurse into GP practices, and enhanced access of patients to community-based evaluation of their CHC disease. Adult patients on OST who attend the practice for any reason during the recruitment period are eligible. A substantial proportion of CHC patients on OST in general practice are not engaged with specialist hospital services but qualify for direct-acting antiviral drugs treatment.¹⁰

Treating CHC among PWID (people who inject drugs) is crucial to achieve the WHO goal of hepatitis C elimination, due to high prevalence and risk of transmission. In a nationwide CHC awareness and case finding campaign in the Netherlands, an intervention targeting PWID was effective and cost-effective, whereas an intervention targeting risk groups in the general population showed only a modest effect and was less likely to be cost-effective.¹¹ A study using a dynamic hepatitis C transmission and liver-disease progression mathematical model to test interventions (including availability of point-of-care RNA testing; increased testing of PWID; and scaling up primary care treatment delivery) concluded that even with unlimited and unrestricted access to DAA treatment, interventions to improve the CHC cascade of care and target PWID will be required to achieve elimination targets.¹²

A number of studies have been conducted in primary care to evaluate the implementation of recommendations from the US Centre for Disease Control (CDC) to conduct routine screening for CHC of birth cohort patients born between 1945 and 1965¹³. In one cRCT, brief education of physicians and alerts imbedded in electronic health records (EHR) improved screening rates in intervention sites¹⁴. In a before and after study quality improvement activities using audit and feedback (informing providers of their personal HCV screening rates relative to the clinic as a whole) as well as EHR alerts provided the most significant improvements in screening rates.¹⁵

Although not in the primary care setting it is worth noting a project in Utrecht which identified untreated patients with positive hepatitis C virus tests from the laboratories of four hospitals and one central laboratory and invited them for re-evaluation with blood tests, liver assessment and possible DAA therapy. The retrieval of previously diagnosed CHC patients through screening diagnostics was deemed feasible and worth pursuing for the elimination of CHC.¹⁶

A meta-analysis of evidence-based interventions addressing CHC screening and treatment initiation published in 2015, before DAAs were introduced, found high rates of uptake and case-finding when interventions target high-risk individuals in specific settings, including patients in a primary care clinic with certified methadone prescribers, with interventions such as provider education with nursing support and people who inject drugs in Needle & Syringe Programs. Programs were found to be generally effective at identifying new cases of CHC and cost-effective when compared to treatment-as-usual, though often they required ancillary structural support to increase testing rates. The review also found that primary care settings represent key opportunities for CHC care linkage interventions, often within clinics that have prolonged engagement with homeless, substance using populations, or PWIDs. None of the included studies assessing treatment initiation were set in primary care.

There is a need for evidence-based interventions to improve case finding and treatment uptake in primary care setting in this DAA era.

NPS MedicineWise educational interventions

Each year NPS MedicineWise designs, develops, implements and evaluates a range of national educational therapeutic programs. Programs are evidence-based and multifaceted. Activities and interventions include educational visiting, case-based meetings, data-driven quality improvement reports and interventions, clinical e-audits, online case studies and online learning, consumer awareness campaigns, and decision-support tools for health professionals and consumers. A total of 29,444 educational visits to primary care were conducted by NPS MedicineWise during 2017-18, including 65% of registered general practitioners.

Further information is available on the NPS MedicineWise website, <http://www.nps.org.au/>.

MedicineInsight practice quality improvement activities

MedicineInsight is a leading large-scale primary care data set of longitudinal de-identified electronic health records (EHR) in Australia. MedicineInsight was initially established by NPS MedicineWise in 2011, with core funding from the Australian Government Department of Health, to collect general practice data to support quality improvement in Australian primary care and post-market surveillance of medicines. The monthly collation of collected data can be analysed for the purposes of improving patient care, quality improvement and evaluation, performing population health analysis, research and developing health policy.

General practitioners who participate in MedicineInsight are given the option of receiving personalised reports to facilitate peer comparison in their practice. MedicineInsight currently generates reports specifically for GPs and practices to address the evidence-practice gaps identified in prescribing in general practice. Participating practices are offered a free in practice meeting to discuss their report and data, and compile an action plan, facilitated by a trained clinical service specialist (the majority of these facilitators are pharmacists). Encrypted patient lists (identified as requiring follow-up at the practice) can be generated by MedicineInsight and, via a secure method of de-encryption that can only occur onsite at the practice, the practice staff can re-identify their own patients' data.

Further information is available in Appendix 1 and online: <https://www.nps.org.au/medicine-insight>

Ethics approval for MedicineInsight

In December 2017, NPS MedicineWise was granted ethics approval for the standard operations and uses of the MedicineInsight database by NPS MedicineWise. This 'umbrella' approval was given by the RACGP NREEC (NREEC 17-017). Projects involving sensitive conditions require separate ethical consideration.

While quality improvement activities are considered a standard use of MedicineInsight data covered by the umbrella ethics approval, we are seeking ethics approval for both the quality improvement program on hepatitis C, as well as the RCT as the project involves patients with a sensitive medical condition (CHC).

2017 NPS MedicineWise Hepatitis C educational and quality improvement program

Between October and December of 2017, NPS MedicineWise delivered an education-based quality improvement intervention to 70 practices participating in the MedicineInsight program and 30 non-MedicineInsight practices. The intervention aimed to improve the management of patients with CHC and was funded by Gilead Sciences. The ethical issues surrounding the delivery of the interventions were considered by BellBerry Limited Human Research Ethics Committee (application number: 2016-11-792, approved 27 April 2017).

After completing the program, the majority of GPs were confident in recalling patients with CHC, confirming diagnosis, deciding which patients could be managed in primary care and deciding when specialist consultation or referral was required. A retrospective cohort study to evaluate this program using MedicineInsight data was considered by BellBerry Limited Human Research Ethics Committee (application number: 2018-10-837, approved 14 November 2018). Data from the MedicineInsight practices who received the intervention in 2017 were compared to data from the remaining MedicineInsight cohort of practices who did not receive an intervention, and served as the control group. The committee considered the evaluation

study fell within NPS MedicineWise's current agreement with the practices who participate in the MedicineInsight program, which explains that the data collected is used for quality improvement activities, research and evaluation projects, which may be funded by government, academic and industry funders (including pharmaceutical companies). Further consent was not required.

The non-randomised, targeted delivery of the intervention resulted in differences between the intervention and control arms, confounding the interpretation of the findings. The current planned study will overcome this limitation by delivering the intervention according to a pre-planned randomised procedure. The only difference between this current study and the previously approved evaluation study using MedicineInsight data is that delivery of the education is being randomised, rather than targeted.

What this project adds

There have been a number of educational interventions directed at GPs since the listing of DAA on the PBS in March 2016. These range from local one-off information sessions (such as a presentation by a specialist) to more intensive and ongoing education with links to specialist support such as education provided by ASHM or through project ECHO <http://www.swsphn.com.au/hepatitis-c>. To our knowledge none of these interventions have been evaluated by RCT design to assess the impact of the education on GP prescribing. In the context of falling treatment numbers in Australia and a worldwide push to eliminate HCV driven by WHO, there is a pressing need to show which interventions are of benefit in increasing GP prescribing for CHC and increasing testing and diagnosis of CHC in patients at risk. The planned retrospective cohort study of the NPS MedicineWise 2017 hepatitis C educational intervention using MedicineInsight data will provide some information on the impact of small-group in-practice education, but is limited by its non-randomised design.

NPS MedicineWise plans to design, develop and implement an educational and quality improvement program in 2019 to support GPs in the diagnosis and management of CHC. The program will build on the NPS MedicineWise program delivered in 2017 and reflect key changes in the guidelines and new treatments available. The program will focus on diagnosis and pre-treatment assessment of patients with hepatitis C and the identification of patients who may be at risk of infection. The program will cover the appropriate use of medical tests and medicines, and link GPs to their local specialist centre (where available) or an Australian specialist (via the REACH-C network) who can provide ongoing support, mentoring and approval for HCV prescribing in those GPs new to CHC prescribing. The program will be delivered to about 200 general practices (approximately 1000 GPs) across Australia. The design and delivery of this quality improvement program will be supported by data-based insights drawn from NPS MedicineWise's national general practice data program, MedicineInsight. An audit and feedback tool will also be developed and made available for GPs to encourage systematic recall of patients with possible or confirmed CHC.

A cluster randomised controlled trial (cRCT) will be used to evaluate the benefit of the quality improvement intervention within MedicineInsight practices. To our knowledge there are no other randomised controlled trials evaluating the effectiveness of an educational intervention on treatment initiation of DAA therapy in primary care. The evaluation of this project will build on the 2017 NPS MedicineWise Hepatitis C educational program, with more rigorous evaluation.

The results of this trial will help inform future initiatives in Australia as well as internationally to continue the treatment momentum to help eliminate CHC.

The design of the cRCT protocol has been provided by an independent Research Advisory Group, principal investigators, with expertise in:

- Treatment of CHC in general practice
- Specialist CHC practice
- CHC clinical trials
- cRCT within cohorts
- Large data sets

2. FUNDING

Funding for this project is supported by an independent educational grant from Gilead Sciences Pty Ltd to VentureWise Pty Ltd. The grant contract can be provided upon request. VentureWise Pty Ltd is a wholly owned subsidiary of NPS MedicineWise and have commissioned NPS MedicineWise to design, develop, implement and evaluate the project which will be conducted with complete independence from Gilead Sciences. Gilead Sciences will not have input into the design of the study or education, membership of the expert advisory group, content of the project, randomisation, participating practices, implementation of the program, data collection, statistical analysis, evaluation or resultant publications.

3. PROTOCOL

3.1. Aims

- ▷ To evaluate the effectiveness of the NPS MedicineWise educational intervention to enhance case finding, assessment and treatment of patients with CHC using MedicineInsight data.

3.2. Hypothesis

- ▷ Using a cluster randomised controlled trial design, we will test the hypothesis that compared to control practices, those practices randomised to receive the NPS MedicineWise educational intervention will have a higher number and proportion of patients with CHC initiating DAA therapy and a higher number of patients being tested with an HCV (hepatitis C virus) RNA qualitative or quantitative PCR test for diagnosis.

3.3. Objectives

Primary objective

The primary objective is to evaluate the number of new prescriptions for DAA therapy over 6 months in practices who received the intervention as compared to control practices who did not receive the intervention.

Secondary objectives:

- ▷ To evaluate the proportion of patients with untreated CHC who initiate DAA over 6 months in practices who received the intervention as compared to control practices who did not receive the intervention.
- ▷ To evaluate the number of patients with untreated CHC who visit the practice in the 6 month period following the educational intervention compared to the number in control practices who did not receive the intervention.
- ▷ To evaluate the number and proportion of patients with untreated CHC who visit the practice in the 6 month period following the educational intervention and have a quantitative or qualitative HCV RNA test recorded compared to control practices.
- ▷ To evaluate the number and proportion of patients with untreated CHC who visit the practice in the 6 month period following the educational intervention and have a HCV genotype test recorded compared to control practices.

Tertiary objectives:

- ▷ To explore the feasibility of estimating the proportion of patients with undetectable HCV RNA results 3-6 months (SVR12) after treatment with DAA (dependent on the quality of pathology test results for HCV RNA).
- ▷ To explore the practice and patient factors associated with a positive response to the intervention.

3.4. Rationale

- ▷ With GPs now eligible to prescribe the new highly efficacious DAA medicines for CHC, and new guidelines available, there is a pressing need to support GPs, and implement new shared care models to improve HCV management and treatment.
- ▷ NPS MedicineWise is well placed to provide educational support via the national field force of NPS clinical service specialists (CSS) and to evaluate the effectiveness of the program to inform future programs.

- ▷ The project aims to support the goal of Australia's National Hepatitis C Strategy, in particular the objective to increase access to appropriate management and care for people with chronic hepatitis C.¹⁷
- ▷ To our knowledge there are no other randomised controlled trials evaluating the effectiveness of an educational intervention treatment initiation of DAA therapy in primary care. The results of this trial will help inform future initiatives in Australia as well as internationally to continue the treatment momentum to help eliminate CHC.

3.5. Methodology

3.5.1. Study type

This is a hypothesis testing interventional study, where the intervention is being delivered to general practices that have already consented to participate in the MedicineInsight program and whose routine electronic health record (EHR) data is collected by NPS MedicineWise on a regular basis.

3.5.2. Study design

The study will be a cluster randomised controlled trial (cRCT), with general practices who participate in MedicineInsight as the unit of randomisation.

3.5.3. Eligibility criteria

Practice sites:

1. Participates in the MedicineInsight Program and meets MedicineInsight data quality requirements
2. Did not participate in the 2017 NPS MedicineWise educational program on Hepatitis C
3. Located in a geographical area serviced by one of the CSS field force delivering the intervention
4. Use of Medical Director or Best Practice for EHR management
5. Has 5 or more patients with possible or confirmed CHC* who visited the practice at least once in the 2 years prior to randomisation

*As part of a previous project related to hepatitis C, we have developed a set of search algorithms that scan the data in MedicineInsight for terms that indicate confirmed or possible CHC. These algorithms and terms are outlined in detail by Chidwick *et al* (2018)¹⁸. The algorithms search for a patient's most recent docle and pyefinch codes as well as free text expressions pertaining to hepatitis C in clinical system records that describe reason for encounter, reason for prescription, or diagnosis. Additional criteria are applied to confirm CHC in patients whose most recent status is indeterminate, including prescriptions, tests, and complications related to CHC.

Exclusion criteria

Practices that withdraw their consent to participate in this study, or the MedicineInsight program, before or during the period of analysis will not be included in this study. Practice-level withdrawals are rare in MedicineInsight. Data for patients who opt-out from the program will be excluded from the study.

3.5.4. Site recruitment

The sampling frame for randomisation will be the general practices participating in the MedicineInsight program and located in the geographical regions served by the 8-12 field based Clinical Service Specialists (CSS) who will be delivering the educational intervention. These general practices have already consented to participate in the MedicineInsight program, and were informed upon joining, and at regular intervals since, that their practice data is used by NPS MedicineWise to develop educational quality improvement activities on various topics and to evaluate these activities. As such all EHR data, including the data required for the evaluation of this intervention, is already collected from these practices on a regular basis. Furthermore a letter will be sent to all eligible MedicineInsight practices to inform them that NPS MedicineWise plans to deliver a quality improvement activity on the management of patients with CHC and this educational activity

will be evaluated using data collected as part of the MedicineInsight program, using a randomised controlled trial design. As such they may or may not be invited to participate depending on the random selection process. They will have the opportunity to opt out of this specific trial and remain in the MedicineInsight program.

Appendix 2 contains the information sheet and opt out form which will be provided to eligible MedicineInsight practices by post and email. A follow-up phone call one week after the mail-out will be carried out by the NPS MedicineWise recruitment team to ensure practices received the information materials and have the opportunity to answer any questions. Practices will be provided with 1 month to opt out of the trial before randomisation and recruitment will commence. Should a practice choose to opt-out of the RCT after this period their data will not be analysed in this study

Non-MedicineInsight practices to be offered the intervention

An additional 50 practices which are not involved in MedicineInsight will also receive the intervention. These additional 50 “non-MedicineInsight” practices will not be included in the evaluation, and as they are not part of MedicineInsight their data will not be collected. These practices will solely be participating in the quality improvement activity (not the evaluation of the intervention) and will be targeted based on area prevalence statistics. However, as the educational intervention involves national level indicators for the care of patients with chronic hepatitis C, based on aggregated MedicineInsight data, we also seek ethics approval for this component of the project.

3.5.5. Randomisation

300 MedicineInsight practices (clusters) will be randomised in a 1:1 allocation to receive the NPS MedicineWise educational intervention. Clusters will be stratified according to high (>50) and medium/low (5-50) caseloads of patients with CHC. Block randomisation will be performed by a statistician not involved in the study. Outcome analyses will be conducted blinded to intervention allocation.

3.5.6. Intervention group

The intervention arm will be invited to receive the 1 hour small group educational intervention from NPS MedicineWise summarised below. Reasons for refusing the intervention will be recorded. All analyses will be conducted on an intention to treat basis, with per protocol analyses as secondary.

The intervention: General practice based educational program

An educational program on the management of CHC will be designed and implemented with advice from members of the Expert Advisory Group, building on the NPS MedicineWise program delivered in 2017 and reflecting key changes in the guidelines and new treatments available. The NPS MedicineWise field force of CSS will provide in-practice, multidisciplinary, small group meetings to deliver the medical education. Delivery of this program will be targeted to MedicineInsight practices with 5+ patients with CHC who visited in the 2 years prior to randomisation and to 50 non-MedicineInsight practices in geographical areas identified as having higher populations of people living with hepatitis C.

Each meeting will involve a 1 hour facilitated discussion among the health professionals at the practice about the treatment and management of patients with CHC, using data insights from MedicineInsight and led by a CSS from NPS MedicineWise. The medical education program will support GPs to take an active role in identification, diagnosis and management of people with CHC including treatment or referral as appropriate. The program will aim to raise awareness, provide education and increase confidence in management of CHC. The program will also aim to facilitate links between GPs and specialists who can provide approval for treatment and support GPs while they increase their experience in CHC management. It will include education on the following:

- Identification, screening and diagnosis of CHC
- Pre-treatment assessment including assessment for co-morbidities, prior treatment history, drug interactions, treatment compliance,

- appropriate assessment of liver disease
- management options for CHC and the patient and medicine factors that affect treatment selection and efficacy.
- Monitoring and follow up including testing for sustained viral response at 12 weeks post treatment (SVR12)

This educational visit will give practices the opportunity to reflect on their practice and identify which areas require additional or continued attention. The visit will explore opportunities to improve management of patients with CHC and the actions required.

Practices that participate in MedicineInsight will receive a personalised 'audit and feedback' report that includes data specific to their practice and which benchmarks this information against the average of all MedicineInsight practices. Practices that do not participate in MedicineInsight will receive a generic report with data for the average of all MedicineInsight practices.

Both types of practice reports will summarise the following types of characteristics:

- ▷ the number of patients with possible or confirmed CHC who visited the practice at least once in the previous two years
- ▷ the age and sex distributions of patients with CHC
- ▷ the number of patients with confirmed CHC co-infected with hepatitis B or HIV
- ▷ the number of patients with confirmed CHC with liver cirrhosis or hepatocellular carcinoma co-morbidities
- ▷ the number of patients with possible or confirmed CHC who had a qualitative RNA test
- ▷ the number of patients with possible or confirmed CHC who had a quantitative RNA (viral load) test
- ▷ the number of patients with confirmed CHC who had a genotype test
- ▷ The number of patients with confirmed CHC with a platelet to AST ratio (APRI) of ≥ 1
- ▷ the number of patients who received treatment for Hepatitis C with a DAA

In addition to the feedback reports, the education will include a case study, educational materials developed by ASHM, and an action sheet completed by the CSS during the visit. MedicineInsight practices will also receive a patient list to re-identify at the practice – this list identifies patients for potential follow up based on measures in the Practice report and as advised by the Expert Advisory Group. The patient list is de-identified, until it is installed in the practice.

All practices will have an online audit and feedback/practice review tool made available following the practice visit, to support them in their follow up and initiation of CHC care. Non-MedicineInsight practices will also be able to participate in the audit activity.

NPS MedicineWise will apply to RACGP for continuing professional development credits to be made available for these activities.

3.5.7. Control group

MedicineInsight practices allocated to this arm will continue usual practice without being offered the educational intervention from NPS MedicineWise. As with the intervention arm, practices participating in any Quality Improvement activities for the management of CHC will continue participation as usual.

3.5.8. Study time period

Intervention cohort

- ▷ Six months after the date the practice receives the educational intervention (the index date). If the practice declines the intervention the index date will be the date of randomisation. Six months is considered sufficient duration for significant outcomes to be detected and short enough to avoid contamination by other initiatives.
- ▷ All available medical history in the database will be used to identify people living with CHC.

Control cohort

- ▷ Six months after the date of randomisation (the index date).
- ▷ All available medical history in the database will be used to identify people living with CHC.

3.5.9. Data sources

The analysis will be based on the MedicineInsight data, which is a large computerised database of anonymised primary care medical records described in Appendix 1. Data will be extracted from the MedicineInsight database uniformly for control and intervention practices by an analyst who is blinded to the intervention status of the practice. Data will be extracted for included practices and patients from all relevant data fields including patient demographics, diagnoses and symptoms, observations, pathology test results, and prescriptions. Data will only be extracted and analysed by NPS MedicineWise staff in the MedicineInsight team who have received the mandatory data governance training. The data for analyses will be stored on MedicineInsight secure SAS servers and can only be accessed by MedicineInsight staff on password protected computers.

Patients will be included in the analysis if they meet the below criteria:

- ▷ Attendance at an eligible MedicineInsight practice site at least once during the 24 month period before the index date or during the 6 month period after the index date.
- ▷ Aged 18 years or over and therefore eligible for PBS subsidised DAA therapy
- ▷ Have a record of confirmed or possible CHC and have no record of the infection having resolved spontaneously, or being cured prior to the index date
- ▷ No recorded prescription for DAA therapy prior to the index date.

Pre-randomisation:

Prior to randomisation eligible practices will be identified using MedicineInsight data based on the criteria described in section 3.5.3

Randomisation:

Sites will be randomised to intervention or control. Personalised audit and feedback practice reports will be produced for practices in the intervention arm using MedicineInsight data. Intervention sites will be invited to receive the educational session about CHC (the intervention) and reasons for refusal will be collected. Control sites will not be contacted. The interventions will be delivered over a 2-3 month period.

End of intervention period:

At the end of 9 months (or 6 months after the last intervention is delivered) routinely collected data from the MedicineInsight program will be analysed for both study arms.

3.6. Primary outcome

The number of patients with a new prescription for DAA therapy (Table 1) in the 6 months after the index date.

3.7. Secondary outcomes

- ▷ The proportion of patients with untreated CHC who visit the practice and initiate a DAA in the 6 months after the index date
- ▷ The number of patients with untreated CHC who visit the practice in the 6 months after the index date
- ▷ The number and proportion of patients with untreated CHC who have a quantitative or qualitative HCV RNA test recorded in the 6 months after the index date
- ▷ The number and proportion of untreated CHC who have an HCV genotype test recorded in the 6 months after the index date

3.8. Tertiary outcomes

- ▷ The proportion of patients treated with DAA with undetectable HCV RNA results 3-6 months after treatment (SVR12)

TABLE 1: DIRECT-ACTING ANTIVIRALS (DAA) RELEVANT TO THE PRESENT STUDY.

Medicine Active ingredient	Brand name
Daclatasvir	Daklinza
Glecaprevir with pibrentasvir	Maviret
Grazoprevir with elbasvir	Zepatier
Ledipasvir with sofosbuvir	Harvoni
Paritaprevir with ritonavir, ombitasvir and dasabuvir	Viekira Pak
Paritaprevir with ritonavir, ombitasvir, dasabuvir, ribavirin	Viekira Pak-RBV
Sofosbuvir	Sovaldi
Sofosbuvir with velpatasvir	Epclusa
Sofosbuvir with velpatasvir and voxilaprevir	Vosevi
Ribavirin (non-DAA adjuvant therapy)	

3.9. Covariates (predictors of response)

- ▷ Size of the practice ie the total number of regular patients (3 visits in the last 2 years)
- ▷ Caseload of hepatitis C patients (high, medium or low) at the practice
- ▷ The number of staff members who attended the educational visit
- ▷ The number of GPs who attended the educational visit
- ▷ Practice successfully re-identified the patient list for follow-up
- ▷ Practice state
- ▷ Practice region
- ▷ Practice socioeconomic status (SES)
- ▷ Existing DAA prescribers in the practice
- ▷ Existing OST prescribers in the practice

3.10. Sample size considerations

Randomisation of 300 MedicineInsight practices (150 per arm) will provide 90% power at the 0.0125 significance level to detect a ≥ 1.5 times higher average number of DAAs per practice and a $\geq 6\%$ absolute higher proportion of patients with CHC prescribed a DAA among practices receiving the educational visit. The following assumptions are based on the 2017 educational visiting program and more recent estimates from a post-marketing surveillance report using MedicineInsight data on the use of DAAs for the Department of Health.

1. Cluster size of eligible population will range from 5 patients with possible or confirmed CHC in a low caseload practice through to 200 patients in a high caseload practice. A mean average cluster size of 20 (SD: 19) is assumed.* Methods to account for variable cluster size are recommended when cluster size variability is large, i.e. the coefficient of variation of cluster size, defined as the ratio of the standard deviation of cluster size S_n to mean cluster size n , is greater than 0.23 – here it is 0.952.
2. The mean (SD) and proportion of patients with confirmed CHC prescribed DAA therapy per control practices is 1 (2) and 8% respectively.
3. The mean (SD) and proportion of patients prescribed DAA therapy in intervention practices is 1.5 (2) and 14%, respectively.
4. An intra-class correlation coefficient of 0.05 for the primary outcome based on previous studies⁹ and analysis of data from the 2017 evaluation, with a resultant design effect of 2.45 to accommodate variation in prescribing rates across practices.

5. A conservative refusal rate of 33% (anecdotal reports from previous programs estimate that roughly 25% of MedicineInsight practices invited to participate in education programs might be expected to refuse)
6. A Bonferroni correction has been applied to account for testing multiple hypotheses – therefore the level of significance will be $p=0.0125$ (instead of 0.05).

Clusters will be stratified on caseload of patients with chronic HCV– high, low. Data analysis will be performed on an intention-to-treat basis using standard techniques for cluster randomised designs such as mixed models and generalised estimating equations.

3.11. Data and statistical analysis

- ▷ The proportion of confirmed CHC patients treated with a DAA, compared between intervention and control arms as a rate ratio, will be estimated in a negative binomial model, adjusted for whether an individual’s practice is high caseload or not, and whether that practice has at baseline a high DAA prescribing rate or not. This regression model accommodates overdispersion and variation in the outcome measure between GP practices. This approach will be adapted to the secondary outcome measures, and also to estimate the risk difference between intervention and control arms for the primary outcome measure. These analyses will follow the intention-to-treat principle, with practices being analysed in the arms to which they are randomised.
- ▷ To help us describe predictors of good response linear regression modelling will be used to assess the effect of the covariates of interest on the impact of the intervention.
- ▷ We will test the robustness of our results by varying some of the parameters used to select the patient population and the time step over which the analysis is performed.
- ▷ Data management and analyses will be conducted with SAS ® Enterprise Guide 7.1 (Cary, NC USA, 2017).

TABLE 2: NUMERATORS AND DENOMINATORS FOR THE STUDY OUTCOMES

Outcome	Numerator	Denominator
Number initiated on DAA therapy	The number of patients with confirmed CHC who were prescribed a DAA therapy during the 6 month study period	n/a
Proportion initiated on DAA therapy	The number of patients with confirmed CHC who visited the practice at least once and who were prescribed a DAA therapy during the 6 month study period	The number of patients with confirmed CHC who visited the practice at least once during the 2 years prior to the study or during the 6 month study period
Number tested for CHC with a quantitative or qualitative HCV RNA test	The number of patients with possible or confirmed CHC who had a HCV RNA test recorded during the 6 month study period	n/a
Proportion tested for CHC with a quantitative or qualitative HCV RNA test	The number of patients with possible or confirmed CHC who visited the practice at least once and who had a quantitative or qualitative RNA test recorded during the 6 month study period	The number of patients with possible or confirmed CHC who visited the practice at least once during the 2 years prior to the study or during the 6 month study period

Assessment of hep c genotype	The number of patients with confirmed CHC who visited the practice at least once and who had a HCV genotype test recorded during the 6 month study period.	The number of patients with confirmed CHC who visited the practice at least once during the 2 years prior to the study or during the 6 month study period
Encounter rate for patients with chronic hepatitis C	The number of patients with possible or confirmed CHC who visited the practice at least once during the 6 month study period	

3.12. Limitations and strengths of the study design, data sources and analytical methods

MedicineInsight includes routinely collected anonymised electronic health record data from general practices who have consented at a practice level to provide data on a monthly basis. Like all large administrative health datasets, there are a number of limitations that relate to the purpose for which the data was originally collected and the governance of the data.

In Australia, the use of electronic health records in general practice is still in an early stage. These systems have changed from electronic prescribing systems to electronic health records with little regulation or support to ensure that the data entered and maintained in these systems is of high quality and reliable. There have been some improvements since “My Health Record” and its predecessor were initiated. MedicineInsight also encourages its practices to maintain complete and high quality records. The continuing improvement is expected to increase the identification of chronic hepatitis C cases and relevant investigations.

MedicineInsight includes information on prescriptions provided by the GP but not what was dispensed, and/or taken by the patient. MedicineInsight does not include comprehensive records of medicines prescribed by specialists unless there is information recorded by the practice in a field collected by MedicineInsight. Therefore we might underestimate the proportions ever on a treatment for CHC.

Results of laboratory tests ordered by the GP are commonly added to the patient record via electronic links from laboratories. Data fed back to the GP from other sources may also be entered or scanned onto the patient record by practice staff; these data might include information from secondary care such as key diagnoses, discharge data from hospitals, or follow-up information from specialist clinics. The GP is also able to make additional un-coded notes and observations about patients as free text in ‘progress notes’. This often contains patient-identifying information and is not collected by MedicineInsight.

While comprehensive records of pathology tests orders are available for most patients in MedicineInsight, technical issues sometimes occur with the electronic transfer of test data to the practice’s clinical information system (due to incompatible systems or user preferences) so a small proportion of test records, although visible at the practice, may not be included in MedicineInsight data. Tests recorded by GPs only in free text fields that aren’t collected by MedicineInsight, such as progress notes, won’t be captured in these analyses.

Of note, test results of a sensitive nature may be excluded from electronic transfer of results into the system (in the case of a user preference activated by practice staff). As such in some cases we may be able to see a hepatitis C serology test was ordered but not the actual results.

4. ETHICAL CONSIDERATIONS

4.1. Requirement for independent ethics committee approval

In November 2018 the Independent MedicineInsight Data Governance Committee (DGC) will consider this current proposal to evaluate the program. Approval from the DGC is required to enable access to and use of MedicineInsight data for this project and may be contingent on ethics approval.

While quality improvement activities are considered a standard use of MedicineInsight data covered by the aforementioned umbrella ethics approval, we are seeking ethics approval for this particular project which involves patients with a sensitive medical condition and a cluster RCT.

The aim of the project is to develop, implement and evaluate a quality improvement program to improve the care and management of people with CHC via targeted GP medical education to practices contributing to MedicineInsight (using their own practice level data presented in a practice specific report), and to non-MedicineInsight practices (using relevant de-identified aggregated data from the MedicineInsight practices). The NPS MedicineWise field force of clinical service specialists will deliver the medical education via in-practice multidisciplinary small group meetings.

Non-MedicineInsight practices to be offered the intervention

An additional 50 practices which are not involved in MedicineInsight will also receive the intervention. These additional 50 “non-MedicineInsight” practices will not be included in the evaluation, and as they are not part of MedicineInsight their data will not be collected. These practices will solely be participating in the quality improvement activity (not the evaluation of the intervention) and will be targeted based on area prevalence statistics. However, as the educational intervention involves national level indicators for the care of patients with chronic hepatitis C, based on aggregated MedicineInsight data, we also seek ethics approval for this component of the project.

A range of potential ethical issues associated with this project are discussed below.

4.2. Voluntary participation

A signed agreement is required from the general practice owner (or authorised representative) for a general practice to participate in MedicineInsight. The agreement includes information about how the data will be used including approved third party use. The Practice information is included with this application and states the following:

How does MedicineInsight use data collected from this practice?

The data collected from this general practice is used by us to provide prescribing, data quality and clinical activity reports to your practice.

We also anonymise the data so that it does not identify the practice, and combine it with data from other participating practices, and use that data for research and evaluation purposes, including:

- *chronic disease and other conditions*
- *the quality use of medicines such as antibiotics*
- *post market surveillance of medicines*
- *delivering medical education; and*
- *supporting evidence for listing on the Pharmaceutical Benefits Scheme.*

From time to time we will undertake projects funded by other organisations, including State and Commonwealth government departments and agencies, Primary Health Networks, medical colleges, not-for-profit organisations, and pharmaceutical and health insurance organisations.

When practices join MedicineInsight they agree to inform patients of a practice's participation in MedicineInsight, the scope of the use of the data and what that means for personal information. The patient information states the following:

How does MedicineInsight use the information?

We use the information to improve the quality of health care provided to you, for health research, and to inform health policy. We analyse and report on the usage and safety of medicines (eg medicine side effects), and other topics such as acute conditions (eg cold and flu) and chronic conditions (eg diabetes, asthma), including sensitive and notifiable conditions (eg hepatitis C and HIV). Sometimes these activities are conducted with, and funded by, third parties such as government departments, regulatory authorities, universities, medical charities, pharmaceutical companies or insurance companies.

Patients are not required to give written consent due to the non-identifiable nature of data collection. However, participating practices are required to display in their waiting rooms a poster and information leaflets describing the MedicineInsight program, along with opt out forms. Patients can opt out of the program if they do not wish to participate by a process handled independently at the practice.

The patient opt-out form states the following:

- *I understand that if I opt-out, the practice will stop releasing my non-identifiable information to MedicineInsight.*
- *I understand that under the Australian Privacy Act (1988), NPS MedicineWise has the authority to retain and use non-identifiable information already collected.*

The Practice Agreement, Patient Information and Opt-out Form are included with this application.

NPS MedicineWise's current agreement with the participating practices does not specifically include evaluation using a randomised controlled trial (RCT) design. The agreements with the practice stipulate that from time to time, NPS may offer the practice an opportunity to participate in a defined project such as this trial and their Practice Data will be used to determine if the practice meets the criteria to participate. As RACGP have outlined this is a clinical trial and aligning with our practice agreements, we should inform participating practices of "defined projects" and provide them the opportunity to not participate and still remain in the MedicineInsight program.

For this trial a letter will be sent to all eligible MedicineInsight practices to inform them that NPS MedicineWise plans to deliver a quality improvement activity on the management of patients with CHC and this educational activity will be evaluated using data collected as part of the MedicineInsight program, using a randomised controlled trial design. For this trial, they may or may not be invited to participate depending on the random selection process. They will have the opportunity to opt out of participating in this specific trial. It will be made clear to each practice invited that choosing to not participate in this trial will not impact their ability to remain in the MedicineInsight program.

Appendix 2 contains the information sheet and opt out form which will be provided to eligible MedicineInsight practices by post and email. A follow-up phone call one week after the mail-out will be carried out by the NPS MedicineWise recruitment team to ensure practices received the information materials and have the opportunity to answer any questions. Practices will be provided with 1 month to opt out of the trial before randomisation and recruitment will commence. Should a practice choose to opt-out of the RCT after this period their data will not be analysed in this study.

4.3. Data security

MedicineInsight utilises a third party data extraction tool which extracts, de-identifies and securely transmits whole of practice data from the GP Clinical Information System to a secure data repository. Patient information is compiled and encrypted with password protection during its transfer from the practice to NPS MedicineWise. This ensures the data cannot be accessed by unauthorised users. The data is stored in the NPS MedicineWise data repository/warehouse at a secure data centre in NSW.

We have implemented security and data governance measures to ensure that data held by MedicineInsight cannot be accessed by any non-approved person either within or external to NPS MedicineWise. The data remains secure during transfer, storage, analysis and reporting. Only restricted authorised staff in the NPS MedicineWise team will have access to the MedicineInsight raw data which is stored on the MedicineInsight Secured server, which is isolated from the organisation's main server.

4.4. Confidentiality

All data extracted from general practices are de-identified patient data, meaning that no person external to the practice has access to patient details. Patient level data is de-identified 'at source' meaning the patients' personal identifiers such as name, date of birth, address are not extracted by the tool (although year of birth and postcode are extracted enabling the calculation of age and SEIFA). The MedicineInsight data collection tool installed at the practice automatically removes information that could identify a patient before the information is collected by NPS MedicineWise. A patient record is given a unique identifier so that the impact of any healthcare provided to that patient can be tracked over time. Practice staff are able re-identify patients by unlocking the unique identifier at the practice should they need to follow up individual patients after receiving a MedicineInsight report. The process of collecting patient data achieves a data collection that meets the definition of non-identified data in NHMRC National Statement on Ethical Conduct in Human Research^{Error! Bookmark not defined.} [chapter 3.2, p.27].

Authorised persons within NPS MedicineWise have access to the practice and GP information. This is for the purposes of administering MedicineInsight, providing feedback on prescribing, planning and delivering clinical activities and recording the award of continuing professional development (CPD) points. No third party has access to information that could identify individual practices or GPs.

To avoid the possibility of unintentional (deductive) disclosure of patients, providers and general practices, confidentialisation of data is routinely carried out at the reporting stage. This involves the suppression of small cell numbers, or the aggregation of results to a higher level.

5. PROJECT TIMELINES

Milestone	Duration
Design educational quality improvement program, including data driven MedicineInsight audit and feedback practice reports based on guidelines and previous 2017 education program	October 2018 to March 2019
Ethics approval and Data Governance approval	November 2018 to March 2019
Randomise eligible MedicineInsight practices to intervention or control arm	April 2019
Invite practices randomised to the intervention arm to receive the NPS MedicineWise educational visit	April to June 2019
Build MedicineInsight audit and feedback practice reports for practices in the intervention arm	April to May 2019
Intervention period – conduct practice visits	July to September 2019
End of study: quantitative analyses conducted using routinely collected MedicineInsight data	April to May 2020
Manuscript preparation and submission	May to June 2020
Dissemination of results	July to September 2020

6. PUBLICATION POLICY AND DISSEMINATION PLAN

6.1. Disseminating and communicating project results

The results from this study will be disseminated through presentation at GP and specialist conferences, publication of a manuscript in a peer reviewed journal and via an NPS MedicineWise News article distributed via electronic mail to GPs. Results will also be distributed via the MedicineInsight program electronic mail to participating practices. Members of the Expert Advisory Group will help share results with their networks and a summary of the study will be forwarded to consumer groups such as Hepatitis NSW and other state-based hepatitis organisations for dissemination within their networks.

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APPENDIX 1

NPS MedicineWise

NPS MedicineWise is an independent, not-for-profit and evidence-based Australian organisation, funded by the Australian Government. The organisation was established in 1998 and is committed to the quality use of medicines and medical tests. Each year the organisation designs, develops, implements and evaluates a range of national educational therapeutic programs. Programs are evidence-based and multifaceted. Activities and interventions include educational visiting, case-based meetings, data-driven quality improvement reports and interventions, clinical e-audits, online case studies and online learning, consumer awareness campaigns, and decision-support tools for health professionals and consumers. A total of 29,444 educational visits to primary care were conducted by NPS MedicineWise during 2017-18, including 65% of registered general practitioners.

Further information is available on the NPS MedicineWise website, <http://www.nps.org.au/>.

MedicineInsight program

MedicineInsight is a leading large-scale primary care data set of longitudinal de-identified electronic health records (EHR) in Australia. The MedicineInsight program collates routinely collected EHR data from Clinical Information Systems (CIS) of general practices who have consented to provide data on a continuing basis. Data are not collected from patients who opt out. The monthly collation of collected data (the monthly database build) can be used to analyze the data for the purposes of improving patient care, performing population health analysis and developing health policy.

MedicineInsight was initially established by NPS MedicineWise in 2011, with core funding from the Australian Government Department of Health, to collect general practice data to support quality improvement in Australian primary care and post-market surveillance of medicines. Participating practices receive customised audit and feedback reports, based on their practice data, with peer benchmarking using aggregated data from MedicineInsight practices and guideline recommendations. The reports are delivered via in-practice educational meetings facilitated by NPS MedicineWise Clinical Service Specialists, which inform and enable a practice-wide approach to quality improvement

MedicineInsight utilises a third party data extraction tool (GRHANITE) which extracts, de-identifies, encrypts and securely transmits whole of practice data from the GP Clinical Information System of over 600 general practices. Patient level data is de-identified 'at source' meaning the patients' personal identifiers such as name, date of birth, address are not extracted by the tool (although year of birth and postcode are extracted enabling the calculation of age and Socio-Economic Indexes for Areas [SEIFA]). The data held in the MedicineInsight database are non-identifiable. However, each patient has a unique identifying number which allows all the records (clinical, prescription, referral etc) held in the database for a particular individual over time to be linked. The process of collecting patient data achieves a data collection that meets the definition of non-identified data in the NHMRC National Statement on Ethical Conduct in Human Research. [chapter 3.2, p.27].

The data that MedicineInsight collects from general practice sites include:

- general practice and GP information for the administration of quality improvement activities by NPS MedicineWise
- patient demographic and clinical data entered by GPs and practice staff directly into the system, or collected in the CIS from external sources (eg, pathology test results)
- system-generated data such as start time and date of a patient encounter.

Examples of uses of the MedicineInsight data include:

1. Practice quality improvement programs

General practitioners who participate in MedicineInsight are given the option of receiving personalised reports to facilitate peer comparison in their practice. MedicineInsight currently generates reports specifically for GPs and practices to address the evidence-practice gaps identified in prescribing in general practice. Depending on the consent of the GPs i.e. opt-in or opt-out models, practice reports contain benchmarking information of each GP compared to their practice and to the rest of the other participating practices. Participating practices are offered a free in practice meeting to discuss their report and data, and compile an action plan, facilitated by a trained clinical service specialist (the majority of these specialists are pharmacists). Encrypted patient lists (identified as requiring follow-up at the practice) can be generated by MedicineInsight and, via a secure method of de-encryption that can only occur onsite at the practice, the practice staff can re-identify their own patients' data.

2. Policy development

The MedicineInsight team of epidemiologists, biostatisticians and data analysts produce quarterly reports for the Commonwealth Government Department of Health on medicines use in Australian primary care (eg. antibiotics, antidepressants, biologics). The reports can help the Department understand, for example, how medicines are used in general practice, assess the uptake of new medicines, the effect of policy changes on prescribing, and adherence to PBS guidelines.

Further details about MedicineInsight are available at <https://www.nps.org.au/medicine-insight>

Participation in the program

MedicineInsight is a voluntary, free of charge program offered to general practices in Australia. The recruitment of general practices involves provision of information for GPs and patients about the use of collected data. We require patients to be informed of a practice's participation in MedicineInsight and what that means for personal information. Each participating practice:

- displays a poster to inform patients that their de-identified data will be collected by MedicineInsight
- makes available additional patient information
- provides MedicineInsight contact details (email and phone line), to address any concerns patients may have.

A kit is provided to general practices providing detailed information about MedicineInsight, the agreement and information for patients (attached with HREC application).

A signed agreement is required from the general practice owner for the practice to participate. In signing this Agreement, the general practice authorises NPS MedicineWise to use and share the data extracted from their practice for undertaking projects for research and evaluation purposes, including:

- chronic disease and other conditions;
- the quality use of medicines such as antibiotics;
- post market surveillance of medicines and prescribing gaps;
- delivering medical education to support safe, effective and quality use of medicine; and
- supporting evidence for listings on the Pharmaceutical Benefits Scheme to enable better access to medicines.

Express signed patient consent is not sought as the patient information collected does not identify individual patients. Patients can opt out of the program if they do not wish to participate by a process handled independently at the practice.

Ethics approval for MedicineInsight

The MedicineInsight program, in its pilot stage, was granted ethics approval as a research project by the RACGP National Research and Evaluation Ethics Committee (NREEC) on January 2013 (Reference number NREEC 12 – 011). Once the pilot was completed at the end of 2013, the program transitioned to a quality improvement activity.

In December 2017, NPS MedicineWise was granted ethics approval for the standard operations and uses of the MedicineInsight database by NPS MedicineWise. This 'umbrella' approval was given by the RACGP NREEC (NREEC 17-017). Projects involving sensitive conditions require separate ethical consideration.

MedicineInsight Governance Framework

NPS MedicineWise is the data custodian for the MedicineInsight program. The MedicineInsight program ensures information is collected ethically, legally, securely and confidentially. Our data governance complies with national and state legislations including but not limited to Australian privacy laws and the Australian Privacy Principles.

We have implemented security and data governance measures to ensure that data held by MedicineInsight cannot be accessed by any non-approved person either within or external to NPS MedicineWise. The data collection tool only collects non-identifiable patient data. This means it does not allow personal patient information to be accessed in any way outside of the practice. Any personal information that is collected from practice staff will remain confidential and used for the purposes of administering the quality improvement activities. We store de-identified patient clinical data in a secure data repository. The data remains secure during transfer, storage, analysis and reporting. The process of collecting patient data achieves a data collection that meets the National Statement definition of non-identified data in NHMRC National Statement on Ethical Conduct in Human Research^{Error! Bookmark not defined.} [chapter 3.2, p.27].

NPS MedicineWise may provide de-identified MedicineInsight data to internal and external organisations for research, quality improvement and other purposes, subject to compliance with our data governance framework.

An independent external Data Governance Committee has been established to provide advice to NPS MedicineWise on all aspects related to the data access model.

This project has sought approval from the independent MedicineInsight Data Governance Committee to enable access to and use of MedicineInsight data for this project. The committee is an independent, external committee that has been established to advise NPS MedicineWise on all aspects of the MedicineInsight data access model. The committee consists of external academics, practising GPs and consumer advocates. The group provides guidance and expertise to ensure appropriate governance is in place. Key functions include:

- ▷ advising on data governance as and when it is required by NPS MedicineWise
- ▷ making recommendations on the development of the data access framework and processes
- ▷ providing advice at the request of NPS MedicineWise on specific projects applying for MedicineInsight data
- ▷ reviewing the outcome of approved projects.

APPENDIX 2

DAY MONTH YEAR

The EQUIP-HEPC Study General Practice Information Sheet

Your practice participates in the MedicineInsight program. Please take the time to read this Information Sheet as it provides important information about a randomised controlled study to evaluate one of the MedicineInsight educational quality improvement programs, the benefits of participating, and your privacy.

Study title:

The EQUIP-HEPC trial. A cluster randomized controlled trial of a MedicineInsight educational quality improvement program to improve the diagnosis and treatment of chronic hepatitis C in general practice.

What is MedicineInsight?

MedicineInsight is a national primary healthcare data program developed and managed by NPS MedicineWise, an Australian, independent, not-for-profit organisation. MedicineInsight extracts longitudinal de-identified patient health records from the software healthcare professionals already use to manage patient records and write prescriptions. The data collected through MedicineInsight enables powerful data-driven evidence to be gained into how medicines and medical tests are used. This includes insights to support policy development, and identification of areas of need for new programs. As a participant in the MedicineInsight program, your practice is contributing to helping identify evidence gaps in primary healthcare and to improve clinical practice and health outcomes for Australians.

What is the EQUIP-HEPC TRIAL?

NPS MedicineWise has developed an educational and quality improvement program to support GPs in the diagnosis and management of patients living with chronic hepatitis C (CHC). The design and delivery of this quality improvement program will be supported by data-based insights drawn from the MedicineInsight program. To robustly evaluate the benefit of the quality improvement intervention on case finding and the uptake of treatments for CHC within MedicineInsight practices we are conducting a randomised controlled trial (cRCT) within the MedicineInsight program. The Research Advisory Group has oversight of the study design and reporting of results. The full list of investigators is provided below. The study is registered on the ANZCTR [insert details].

Funding for this project is supported by an independent educational grant from Gilead Sciences Pty Ltd to VentureWise Pty Ltd, part of the NPS MedicineWise group. Gilead Sciences have not, and will not have, input into the design of the study or education, membership of the Research Advisory Group, content of the project, randomisation, participating practices, implementation of the program, data collection, statistical analysis, evaluation or resultant publications.

Investigators' names and contact details:

Principal investigators

- Kendal Chidwick, Epidemiology Lead, MedicineInsight, NPS MedicineWise

- Professor Gregory Dore, Program Head, Viral Hepatitis Clinical Research Program, The Kirby Institute, UNSW Australia, (Research advisory group member)
- Professor Anthony Rodgers, Professorial Fellow, Executive Director's Office, The George Institute for Global Health, Professor of Global Health, Faculty of Medicine, UNSW Sydney, NHMRC Principal Research Fellow (Research advisory group member)
- Dr Min Jun, Senior Research Fellow, Renal & Metabolic Division, Scientia Fellow and Senior Lecturer, Faculty of Medicine, UNSW Sydney, The George Institute for Global Health (Research advisory group member)
- Dr Annie Balcomb, General Practitioner, Suburb (Research advisory group member)

Co-investigators

- Vanessa Simpson, Senior Clinical Program Officer, NPS MedicineWise
- Dr Jeannie Yoo, Medical Advisor, NPS MedicineWise
- Badari Lanka Venkata, Data analyst, MedicineInsight, NPS MedicineWise
- Christopher Gianacas, Biostatistician/Data Analytics Lead, MedicineInsight, NPS MedicineWise
- Tessa Morgan, Epidemiologist, Health Insights & Evaluation, NPS MedicineWise
- Dr Jonathan Dartnell, Clinical Improvement Services Manager, NPS MedicineWise

Ethics and governance approval

This study has been approved by The Royal Australian College of General Practitioners (RACGP) National Research & Evaluation Ethics Committee (NREEC) on the X/X/2019 (Application number: NREEC 18-015) and by the independent Data Governance Committee for MedicineInsight on 3 December 2018 (Application number: 2018-040).

How is this different to your usual participation in the MedicineInsight program?

You will not notice any difference to your normal participation in the MedicineInsight program. This educational activity will be evaluated using data already collected as part of the MedicineInsight program, using a randomised controlled trial design. Depending on the random selection process this practice may, or may not, be invited to receive an educational visit (practice meeting) from one of the NPS MedicineWise Clinical Service Specialists on CHC. This practice will have the opportunity to opt out of this specific study and remain in the MedicineInsight program, via a process described at the end of this form.

What is the purpose of the EQUIP-HEPC study?

This study aims to evaluate the effectiveness of the NPS MedicineWise educational intervention to enhance case finding, assessment and treatment of patients with CHC using MedicineInsight data. CHC is a major public health threat, leading to long term liver disease and mortality, and previously managed primarily by specialists. However, the listing of direct-acting antiviral (DAA) regimens on the Pharmaceutical Benefits Scheme with GP prescribing and the release of Australian recommendations for the management of CHC have expanded the role of GPs in the management of patients with CHC. The new orally administered DAA treatments have shown cure rates of over 95% and are largely well tolerated, however, in 2017 only 15% of the estimated number of people living with hepatitis C in Australia had been treated. More strategies are needed to raise awareness about the need for testing and availability of new hepatitis C treatments to meet the goal set by the World Health Organisation and committed to by Australia – *to eliminate CHC by 2030*.

What will be involved with participation in this study?

The study will be a cluster randomised controlled trial (cRCT), with general practices who participate in MedicineInsight as the unit of randomisation. 300 MedicineInsight practices (clusters) will be randomised to receive the NPS MedicineWise educational intervention or continue with usual care.

Practices randomised to receive the intervention will be invited to receive a 1-hour small group educational meeting from NPS MedicineWise which aims to empower GPs to manage their patients with CHC as a standard part of care. It will use insights from MedicineInsight data to discuss diagnosis of CHC, pre-treatment assessment, appropriate use of medical tests and medicines, and identification of patients who may be at risk of infection. A new audit and feedback tool has been developed to encourage GPs to systematically recall patients with a possible or confirmed infection. Practices allocated to the control arm will continue usual practice without being offered the educational intervention from NPS MedicineWise.

The de-identified electronic health data required for the evaluation of this intervention, is already collected from your practices on a regular basis because of your participation in the MedicineInsight program and according to the agreement. Data will be analysed for included practices from all relevant data fields including patient demographics, diagnoses and symptoms, observations, pathology test results, and prescriptions.

Why has this practice been chosen to participate?

This practice has been selected because it:

- participates in the MedicineInsight program and uses Medical Director or Best Practice for EHR management
- has not already received a CHC educational intervention from NPS MedicineWise
- is in a geographical area serviced by one of the Clinical Service Specialists delivering the intervention
- has 5 or more patients with possible or confirmed CHC who visited the practice at least once in the past 2 years.

Possible benefits of participation

It is estimated that 74% of people living with CHC in Australia remain untreated, at risk of serious long-term liver disease. This trial has the potential to make an important impact on patient care and will provide high-quality evidence to help GPs make important decisions on CHC case finding and management.

To help meet the WHO target of hepatitis C elimination by 2030, there is a need for evidence-based interventions to improve case finding and treatment uptake in the primary care setting. The results of this trial will help inform future initiatives in Australia as well as internationally to continue the treatment momentum to help eliminate CHC.

How does MedicineInsight work?

We have installed a data extraction tool that works seamlessly with your clinical information system, to extract data from your medical records, including patient demographics (e.g. year of birth, sex, postcode) and clinical data entered directly by healthcare professionals (e.g. diagnosis, observations, tests performed). The data is encrypted and securely transmitted to a secure data warehouse managed by NPS MedicineWise. We take robust precautions to protect MedicineInsight data, including encrypting data to government and international best

practice standards. Data is extracted out of office hours so as not to interfere with your day-to-day practice activities.

How is patient privacy protected?

We do not collect identified patient personal information, such as name, date of birth and address. Patient data is de-identified by the data extraction tool before it is securely transmitted to our data warehouse. We adhere to rigorous confidentialisation controls to prevent unintended identification of patient data. To allow us to track data about the patient over time, we tag the de-identified patient data with a unique number. This also enables the general practice to re-identify the patient data in the confines of the practice to help improve the healthcare for that patient. Even though we do not know the identity of the patient, we respect if a patient does not want to participate in the MedicineInsight program. To enable us to respect the choice of patients to opt-out, we require the practice to display a Patient Poster, and provide the patient with an Information Sheet if the patient requests more information. If a patient wishes to opt-out, then a practice staff member will need to change the consent status in the data extraction tool to stop the patient's data from being extracted. Your practice has been provided with copies of the Patient Poster, Information Sheet and instructions on how to opt-out a patient. This is also available at nps.org.au/medicine-insight.

Reporting of study findings

The results from this study will be disseminated through presentation at GP and specialist conferences, publication of a manuscript in a peer reviewed journal and via an NPS MedicineWise News article distributed via electronic mail to GPs. MedicineInsight practices will be notified of any publication of the findings via the regular MedicineInsight newsletter.

To avoid the possibility of unintentional (deductive) disclosure of patients, providers and general practices, confidentialisation of data is routinely carried out at the reporting stage. This involves the suppression of small cell numbers, or the aggregation of results to a higher level.

Your choice

NPS MedicineWise and the investigators respect if you choose not to take part in this study. Choosing not to take part in this study will not preclude a General Practice from participating in the MedicineInsight program or other NPS MedicineWise quality improvement activities including our free educational visits.

The study will commence a month from receipt of this letter and will continue for approximately 18 months. This practice can opt out of this study at any time by filling out the form overleaf and emailing it to MedicineInsight@nps.org.au.

Further information

Call: 1300 721 726

NPS MedicineWise privacy policy available at nps.org.au/privacy.

Email: medicineinsight@nps.org.au

Visit: nps.org.au/medicineinsight

Practice opt-out form

I acknowledge that:

- I have read and understood the EQUIP-HEPC Study General Practice Information Sheet.
 - I have had the opportunity to ask questions about the EQUIP-HEPC study. The study has been explained to me, and my questions have been answered to my satisfaction.
 - I understand that if I opt-out, the practice data collected as part of the MedicineInsight program will not be used for the purposes of the EQUIP-HEPC study
 - I understand that under the Australian Privacy Act (1988), NPS MedicineWise has the authority to retain information already collected.
 - This practices' participation in the MedicineInsight program or other NPS MedicineWise quality improvement activities will not be affected by the choice not to participate in the EQUIP-HEPC Study.
- I want this practice to opt-out of the EQUIP-HEPC Study

Name:

Practice:

Address:

Signed:

Date:

Once completed, please return this form by email to medicineinsight@nps.org.au.