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Utilising provider-parent strategies to improve influenza vaccination in children and adolescents with special risk medical conditions: a randomised controlled trial protocol

Authors

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Abstract

Introduction

Influenza immunisation is a highly cost-effective public health intervention. Despite a comprehensive National Immunisation Program, influenza vaccination in children and adolescents with special risk medical conditions (SRMC) is suboptimal. Flutext-4U is an innovative, multi-component strategy targeting paediatric hospitals, general practice, and parents of children and adolescents with SRMC. The Flutext-4U study aims to assess the impact of Flutext-4U to increase influenza immunisation in children and adolescents with SRMC.

Methods and analysis

This is a randomised controlled trial involving parents of children and adolescents (aged >6 months to <18 years) with SRMC receiving tertiary care at the Women's and Children's Hospital (WCH), Adelaide, South Australia, who are eligible for funded influenza immunisation with a hospital appointment between the start of the seasonal influenza vaccination season and 31 July 2021, their treating general practitioners (GP), and WCH paediatric specialists.

Parents (of children/adolescents with SRMC) are randomised (1:1 ratio) to standard care plus intervention (SMS reminder messages to parents; reminders (written correspondence) for their child's GP from the hospital's Paediatric Outpatients Department) or standard care (hospital vaccine availability, ease of access and reminders for WCH sub-specialists) with randomisation stratified by age-group (<5, 5-14, >14 to <18 years).

The primary outcome is influenza vaccination, as confirmed by the Australian Immunisation Register (AIR).

The proportion vaccinated (primary outcome) will be compared between randomised groups using logistic regression, with adjustment made for age group at randomisation. The effect of treatment will be described using an odds ratio with a 95% confidence interval.

Ethics and dissemination

The protocol and all study materials have been reviewed and approved by the Women's and Children's Health Network Human Research Ethics Committee (HREC/20/WCHN/5). Results will be disseminated via peer reviewed publication and at scientific meetings, professional and public forums.

Trial registration number

Australian New Zealand Clinical Trials Registry (ACTRN12621000463875)

Strengths and limitations of this study

- A randomised controlled trial will allow a determination of the impact of Flutext4U intervention.
- This trial combines primary care and parent-level interventions and was designed for delivery in conjunction with a tertiary-level environment.
- The primary outcome is an objective measure, influenza vaccination receipt, which is confirmed on the Australian Immunisation Register.
- Standard care and intervention arms are independent but parent interaction particularly within subspecialties presents an inherent risk of contamination from intervention arm participants.
- To minimise bias at the tertiary provider level and because randomising sub-specialists would be impractical and risk contamination, both intervention arms will receive standard care.

Introduction

In Australia, influenza is the most common vaccine preventable disease, with direct healthcare costs estimated at >$115 million per annum.(1, 2) Children and adolescents with special risk medical conditions, as defined in the Australian Immunisation Handbook (hereafter-referred to as SRMC) are a priority group for influenza immunisation, because of their significantly greater risk of influenza-associated hospitalisation and death.(3-5) These conditions include: chronic heart, lung, neurological, metabolic, liver or kidney diseases; cancer; diabetes; Down syndrome and underlying immunosuppression.(6) Around half of all children hospitalised with influenza in Australia have at least one SRMC (1, 7), and these children are 30-70% more likely to be admitted to intensive care, require mechanical ventilation, develop bacterial pneumonia, have prolonged hospitalisation or die following influenza infection.(5)

Immunisation is the most effective strategy available to prevent influenza and its complications

Individuals at highest risk of influenza-associated complications have been funded under the Australian National Immunisation Program, to receive the vaccine annually since 2010 (6, 8); with the National Seasonal Influenza Vaccination Program generally commencing in the first month of autumn each year. The influenza vaccine in children can reduce the risk of influenza-associated hospitalisation by 65-70%, including children at increased risk.(9, 10) However, uptake is inadequate in children with SRMC, with coverage across Australia collectively across all SRMC only at 40-52%.(11-13)

Barriers and facilitators to influenza immunisation

Many reasons for low influenza immunisation rates in children with SRMC are

modifiable and include: lack of awareness about recommendations, lack of information, not identifying children as being at risk, concern toward the vaccine/side effects, inconvenience, lack of perceived influenza severity, misinformation, negative social influences, need for a priming dose in children 6 months to 9 years, perceived low efficacy of the vaccine and vaccine access problems.(12, 14-21) Conversely, children are more likely to receive the influenza vaccine if their parents recall the child's specialist recommending it, have adequate awareness and knowledge, believe that the vaccine is effective, safe and easy to access, and if their children are younger in age (<6 years), have previously had influenza vaccine, have more than one SRMC, and that their parents or relatives believe it is necessary along with positive social influences.(11, 13, 15, 18-20, 22, 23)

Interventions to improve influenza immunisation coverage rates

Data informing ways to overcome barriers to vaccine receipt are limited. A systematic review comprising 25 studies assessing strategies to improve influenza immunisation in children with SRMC found that interventions targeting practices, and parent or patients increased coverage by 15% (95%CI: 13-17%) and 57% (52-61%) respectively.(24) However, most studies were conducted in the United States of America (USA), focused only on children with asthma and utilised traditional reminder/recall systems (e.g., written correspondence and telephone calls) that are financially costly, difficult to track receipt and labour intensive to administer. Text-message reminders sent by immunisation providers are a low-cost alternative and have been shown to increase vaccine uptake in some increased-risk groups.(25-28) Notably no studies have investigated the impact of electronic reminders on influenza immunisation coverage in children with SRMC.

Approach to promoting influenza immunisation in children with SRMC

Despite a recommended and funded program targeting children with SRMC, Australia lacks a coordinated implementation-coverage feedback loop, similar to other countries globally.(29, 30) While some hospitals have established services providing immunisation free of charge to children with SRMC, many hospitals and providers recommend that children attend their GP for immunisation, adding to the burden of healthcare visits these families require. Research demonstrates that parents who receive a recommendation from their paediatrician or specialist are up to 16 times more likely to immunise their child.(11, 13) However, less than 58% of parents recall their child's paediatrician recommending influenza immunisation when asked at the end of the season or the following year.(11, 13) Current influenza immunisation protocols often lack consultation with providers and parents and vary significantly, even between departments within the same hospital.(31)

Multi-component interventions are optimal for improving immunisation coverage as they overcome many direct and indirect factors that affect the vaccine decision-making process to address multiple barriers simultaneously. Based in the USA, the Text4Health program implements and evaluates, using randomized control trials, tailored, targeted vaccine text message reminders, with a focus on influenza in urban paediatric and pregnant populations.(27, 28, 32, 33) Other research targeted at the diverse and complex information needs of pregnant women (34, 35) and other special-risk groups (25, 26) demonstrate text-messaging interventions improve coverage. Barriers to influenza immunisation in children with SRMC include: i) a lack of ready access to immunisation services; ii) a lack of healthcare provider recommendation; iii) providers advising against immunisation; iv) safety concerns; v) competing priorities; vi) a lack of understanding of the need to immunise and vii) being unaware of the recommendation to immunise. (11-13, 36) Several barriers

also exist at the provider level with a sense of responsibility, knowledge and confidence of determining 'at risk' conditions, key drivers towards providing a recommendation.(31)

Flutext-4U intervention

The **Flutext-4U** intervention package includes three components which are centrally coordinated. At the tertiary-level: prompt/reminder stickers are placed on medical cases notes and bookmarks at the relevant clinical notes page for notes entry by the clinician to assist hospital specialists to facilitate vaccine recommendation; at the primary care-level: a hard copy communication letter is sent to the child's treating (referring) GP. The written correspondence will advise the GP of the quality improvement initiative to improve low rates of influenza in children with SRMCs and ask them to assist as part of the child's treating team to improve influenza vaccine uptake. The parent-level component includes a text message reminder sent to the child's parent (on behalf of the hospital) advising them that their child/adolescent is eligible for funded influenza vaccine and that they can receive it upon request at the WCH on-site immunisation clinic or at their GP.

Methods and analysis

Study design

This parallel-group randomised controlled trial will measure the impact of the Flutext-4U intervention on receipt of influenza vaccine in children with SRMC, who are patients attending specialist appointments at the Women's and Children's Hospital (WCH), South Australia. Participants will be randomly allocated to one of two combinations of Flutext-4U components. Participants in study arm 1 (standard care) will receive the tertiary-level reminder prompts on medical case notes at outpatient appointments. Study arm 2 will comprise both the primary care and parent-level components, in addition to standard care (Figure 1).

The WCH is one of four public hospitals across metropolitan Adelaide providing care to children and adolescents aged < 18 years and is the state's leading provider of specialist care for children with acute and chronic conditions and the largest maternity and obstetric service. The WCH has 295 beds catering for all paediatric specialties and its Paediatric Emergency Department is a level 1 major trauma centre for children in South Australia. Each year, there are more than 30,000 admissions and about 5,000 births at the hospital. In addition, more than 250,000 people come to the hospital as outpatients.

The study has been approved by the Women's and Children's Health Network Human Research Ethics Committee (HREC/20/WCHN/5). The study will be conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines on Good Clinical Practice. Below, we describe the study protocol.

Primary objective

- Determine the difference in proportion of children and adolescents (aged > 6 months to <18 years) in intervention versus standard treatment arm receiving at least one dose of influenza vaccine by 30/09/2021 (the end of the trial period), with receipt defined as receipt of one or more doses of influenza vaccine, confirmed on the Australian Immunisation Register (AIR) record and parental report.

Secondary objectives

- Determine the difference between intervention and standard treatment arms in the proportion of children and adolescents receiving at least one dose of influenza vaccine during the optimal period (April 1 to June 30).

- Determine the difference between intervention and standard treatment arms in the time from randomisation to vaccination.
- Determine whether the impact of the intervention on the primary outcome is modified by the subgroups: i) age group (<5; 5-14, >14 to <18 years); ii) residential location (metro or regional according to the predefined postcodes for metro and regional areas of South Australia) and iii) paediatric subspecialty (diabetes, neurology, respiratory, gastroenterology, rheumatology, cardiology or other).
- Determine parental acceptability of the SMS intervention.

Procedures

Randomisation

Parents (of children/adolescents) will be randomised to study arm in a 1:1 ratio. The randomisation schedule will be prepared by an independent statistician (not otherwise involved in the conduct or analysis of the trial) and use randomly permuted blocks, stratified by age-group (<5, 5-14, >14 years). The schedule will be provided electronically to the Women's and Children's Health Network (WCHN) ICT Applications System Support staff, who will allocate participants according to the randomisation schedule. The trial statistician will remain blinded.

Study processes

The Flutext-4U Study Coordinator will set up the system to deliver the specialist prompts (all study participants) and liaise with the WCHN ICT Applications System Support staff to set up text message reminders for parents and communication letters for GPs (trial arm #2) to be sent centrally from the WCH. Influenza vaccine signage will be placed around hospital.

Children with SRMC will be identified from the WCH's Outpatient Department's appointment lists and eligibility screening completed with paediatric specialists on a fortnightly basis, using criteria set out in the National Immunisation Program for funded influenza vaccination. A waiver of consent was approved for parents to participate in this trial. Children will be ineligible if they have already received the 2021 influenza vaccine prior to trial commencement (defined as receipt on AIR); are a younger sibling of another trial participant (to ensure parents are not randomised twice); have no listed mobile phone number for parent/ guardian; or have a diagnosis of Cystic Fibrosis, as these children already receive additional vaccine delivery support and influenza vaccine messaging within the WCH environment. Participants (parents) will be randomised to study arm and baseline demographic information will be collected for all parent-child pairs. Demographic data that may impact vaccine coverage will be collected and will include the child's age, gender, Aboriginal or Torres Strait Islander status, medical condition, postcode (to determine SEIFA and residential location, i.e., metro/regional) and previous influenza vaccine receipt in 2019 and 2020 (from AIR records).

Intervention components will be provided, as per study trial arm. Influenza vaccine reminder stickers and bookmarks will be placed on the hard copy paper medical case notes of all study participants. As per study arm, a communication (letter) with the child's treating (referring) GP will advise them that the child is identified as qualifying for funded influenza vaccine and seeking them to assist as part of the child's treating team to improve vaccine uptake. Parental SMS text message reminders will be sent using 'Message Media' software in a non-directive educational approach automatically to the child's parent advising them that their child/adolescent is eligible for funded influenza and where they can receive it. These will be timed to be sent prior to and following scheduled WCH specialist appointments. Each child

will receive a maximum of three SMS reminders, for appointments scheduled between the start of the seasonal influenza vaccination season and the end of July. Text messages will cease if a parent replies to advise that the child is immunised and this is confirmed on the AIR. Text messages will comprise: i) the influenza vaccination message reminder text, ii) an option to reply if the vaccine has been received elsewhere. Parents will be encouraged to engage with their child's specialist, GP or immunisation provider to answer any related questions arising from the influenza vaccination message. Parents may opt-out of further text messages at any time.

At conclusion of the trial, parents in both trial arms will receive an SMS, to ask if the child had received an influenza vaccine in 2021. All collected identifiable data will be securely stored on a database held by the WCHN, with access to the database controlled by password protection. Any data presented will be de-identified prior to presentation.

Patient and public involvement

Patient and public involvement will include influenza vaccine signage designed in conjunction with the Flutext-4U Expert Advisory Group and WCH Consumer Advisory Committee. Parents in both trial arms will receive a parental acceptability survey. Study results will be communicated to key stakeholders and findings will also be disseminated in peer reviewed scientific journals and presented at national and international conferences.

Study monitoring and surveillance

Flutext-4U is a behavioural intervention and as such there are no risks or harms associated with drugs, procedures or devices in this study. The assessment of known potential risks and benefits of the intervention indicate negligible risk through

participation in this study. Any risk of psychosocial distress associated with receiving a vaccine communication (SMS/letter/ reminder) or discussing vaccines is unlikely and is outweighed by the anticipated benefits to the individual and or knowledge that might reasonably be expected from the results. The risk of the intervention is comparable to standard care. A risk assessment and management plan has been developed for all stages of the trial from trial design through to reporting and reflective of the nature of the trial as behavioural intervention. A Trial Management Group comprising the chief investigator, project manager and study coordinator and statistician will closely review all operational aspects of the conduct and progress of the trial and a Trial Steering Committee comprising the investigator team and specialist paediatricians from the study institution, will maintain clinical and ethical oversight.

Sample size and analysis plan

We plan to enrol at least 540 parents of children / adolescents medically at-risk receiving tertiary care at the WCH. In order to have 80% power to detect a 30% relative increase in the percentage of children vaccinated from 40% in the standard care arm to 52% in the trial arm containing all Flutext-4U components, a sample size of 270 children per group is required (two-tailed alpha = 0.05). Previous studies have shown a 30% to 70% relative increase following other immunisation interventions. A 30% relative increase in the percentage vaccinated would be considered clinically meaningful.

All analyses will be undertaken on an intention-to-treat basis according to a statistical analysis plan, pre-specified prior to database lock. For the primary outcome, the number and proportion of participants receiving influenza vaccination in each group will be compared between randomised groups using logistic regression, with

adjustment made for age-group (<5, 5-14, >14 years). The effect of treatment will be described using an odds ratio with a 95% confidence interval. Subgroup analysis will examine the effect of paediatric subspecialty (diabetes, neurology, respiratory, gastroenterology, rheumatology, cardiology or other), age group (<5, 5-14, >14 to <18 years) and residential location (metropolitan, rural according to the predefined postcodes for metro and regional areas of South Australia) on the primary outcome. Secondary analyses will be performed using logistic regression for binary outcomes and a Cox proportional hazards model for time to event outcomes, again with adjustment for age group (<5, 5-14, >14 to <18 years). In all analyses, a two-sided p-value < 0.05 will be used to indicate statistical significance. No adjustment will be made for multiple pre-planned comparisons, as the overall comparison of vaccine uptake is of primary interest.

Discussion

This study will assess the effectiveness of a structured multimodal strategy using evidence-based tools and targeting a paediatric hospital and parents of children with SRMC to increase child influenza immunisation coverage rates. The intervention combines primary care-level and parent-level interventions and was designed for delivery in conjunction with a tertiary-level environment.

Improving immunisation coverage in high-risk populations remains at the forefront of implementation research. Yet, investment into programs and research to ensure funded vaccines are administered to those who need them most has been limited. Only 43.9% (WCH) children with SRMC received influenza vaccine in 2015, despite a funded influenza program for this at-risk group.(11)

Many modifiable barriers to annual influenza immunisation exist and multimodal strategies using: i) practice-level or ii) patient (or parent)-level interventions have

been shown to improve immunisation rates. Employing extensive pilot data obtained by our research from parents and healthcare workers we are uniquely placed to develop, implement and evaluate Flutext-4U. Flutext-4U is a structured multimodal strategy using evidence-based tools and targeting paediatric hospitals and parents of children with SRMC to increase child influenza immunisation coverage rates. Flutext-4U will be implemented at the WCH using a randomised controlled trial design followed by thorough evaluation.

We are mindful of the inherent risk from contamination from intervention arm participants, particularly within medical risk groups due to parent interaction. To minimise bias at the tertiary provider level and because randomising sub-specialists would be impractical, with an almost certain chance of cross-contamination, both intervention arms will receive standard care.

It is also important to collect data on parental acceptability of the intervention as this will have the potential to inform any adaptations to the future implementation of the intervention. Flutext-4U will develop coordinated approaches to immunising children with SRMC and establish the evidence required to optimise paediatric influenza immunisation strategies and campaigns. It will provide a model for future targeted high-risk programs nationally.

If the study demonstrates no negative effects, the intervention will be subsequently implemented for all children with SRMC at the WCH. Any impact on coverage will assist other Australian jurisdictions and national program directors in the implementation of similar programs. Additionally, a focus on developing low-cost, adaptable and scalable methods for improving coverage rates is expected to have implications for many at-risk populations so that the intervention could be adapted and tested in other populations.

Authors' contributions

JT wrote the first draft with assistance from KH, TRS and HM. JF, JC, NS, AT, AK, RC, MF, LF, MD and CB contributed to the manuscript and all authors approved the final version for publication.

Competing interests statement.

JT is an investigator on a project grant sponsored by Industry. Her institution has received funding from Industry (GSK) for investigator led research. She does not receive any personal payments from Industry. HM is an investigator on clinical vaccine trials sponsored by Industry (Pfizer, GSK). Her institution receives funding for Investigator led research from GSK, Pfizer, Sanofi-Pasteur. All other authors (KH, TS, JF, JC, NS, AT, AK, RC, MF, LF, MD, CB) report no conflicts of interest.

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Figure 1: Study design

Footnote: SRMC: special risk medical condition.

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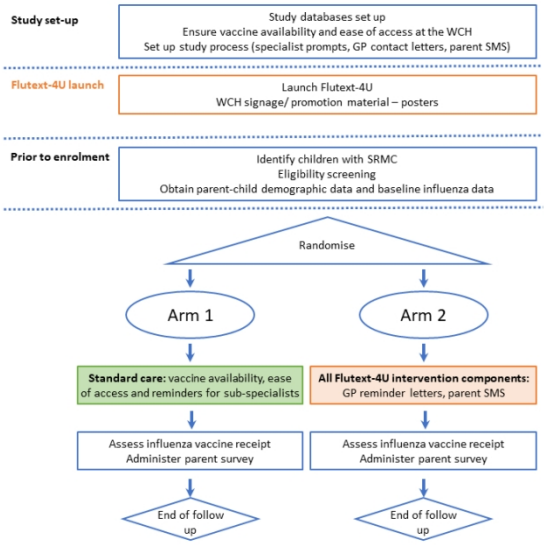

Figure 1: Study design

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Utilising provider-parent strategies to improve influenza vaccination in children and adolescents with special risk medical conditions: a randomised controlled trial protocol

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Abstract

Introduction

Influenza immunisation is a highly cost-effective public health intervention. Despite a comprehensive National Immunisation Program, influenza vaccination in children and adolescents with special risk medical conditions (SRMC) is suboptimal. Flutext-4U is an innovative, multi-component strategy targeting paediatric hospitals, general practice, and parents of children and adolescents with SRMC. The Flutext-4U study aims to assess the impact of Flutext-4U to increase influenza immunisation in children and adolescents with SRMC.

Methods and analysis

This is a randomised controlled trial involving parents of children and adolescents (aged >6 months to <18 years) with SRMC receiving tertiary care at the Women's and Children's Hospital (WCH), Adelaide, South Australia, who are eligible for funded influenza immunisation with a hospital appointment between the start of the seasonal influenza vaccination season and 31 July 2021, their treating general practitioners (GP), and WCH paediatric specialists.

Parents (of children/adolescents with SRMC) are randomised (1:1 ratio) to standard care plus intervention (SMS reminder messages to parents; reminders (written correspondence) for their child's GP from the hospital's Paediatric Outpatients Department) or standard care (hospital vaccine availability, ease of access and reminders for WCH sub-specialists) with randomisation stratified by age-group (<5, 5-14, >14 to <18 years).

The primary outcome is influenza vaccination, as confirmed by the Australian Immunisation Register (AIR).

The proportion vaccinated (primary outcome) will be compared between randomised groups using logistic regression, with adjustment made for age group at randomisation. The effect of treatment will be described using an odds ratio with a 95% confidence interval.

Ethics and dissemination

The protocol and all study materials have been reviewed and approved by the Women's and Children's Health Network Human Research Ethics Committee (HREC/20/WCHN/5). Results will be disseminated via peer reviewed publication and at scientific meetings, professional and public forums.

Trial registration number

Australian New Zealand Clinical Trials Registry (ACTRN12621000463875).

Strengths and limitations of this study

- A randomised controlled trial will allow a determination of the impact of Flutext4U intervention.
- This trial combines primary care and parent-level interventions and was designed for delivery in conjunction with a tertiary-level environment.
- The primary outcome is an objective measure, influenza vaccination receipt, which is confirmed on the Australian Immunisation Register.
- Standard care and intervention arms are independent but parent interaction particularly within subspecialties presents an inherent risk of contamination from intervention arm participants.
- To minimise bias at the tertiary provider level and because randomising sub-specialists would be impractical and risk contamination, both arms will receive standard care.

Introduction

In Australia, influenza is the most common vaccine preventable disease, with direct healthcare costs estimated at >$115 million per annum.(1, 2) Children and adolescents with special risk medical conditions, as defined in the Australian Immunisation Handbook (hereafter-referred to as SRMC) are a priority group for influenza immunisation, because of their significantly greater risk of influenza-associated hospitalisation and death.(3-5) These conditions include: chronic heart, lung, neurological, metabolic, liver or kidney diseases; cancer; diabetes; Down syndrome and underlying immunosuppression.(6) Around half of all children hospitalised with influenza in Australia have at least one SRMC (1, 7), and these children are 30-70% more likely to be admitted to intensive care, require mechanical ventilation, develop bacterial pneumonia, have prolonged hospitalisation or die following influenza infection.(5)

Immunisation is the most effective strategy available to prevent influenza and its complications

Individuals at highest risk of influenza-associated complications have been funded under the Australian National Immunisation Program, to receive the vaccine annually since 2010 (6, 8); with the National Seasonal Influenza Vaccination Program generally commencing in the first month of autumn each year. The influenza vaccine in children can reduce the risk of influenza-associated hospitalisation by 65-70%, including children at increased risk.(9, 10) However, uptake is inadequate in children with SRMC, with coverage across Australia collectively across all SRMC only at 40-52%.(11-13)

Barriers and facilitators to influenza immunisation

Many reasons for low influenza immunisation rates in children with SRMC are modifiable and include: lack of awareness about recommendations, lack of information, not identifying children as being at risk, concern toward the vaccine/side effects, inconvenience, lack of perceived influenza severity, misinformation, negative social influences, need for a priming dose in children 6 months to 9 years, perceived low efficacy of the vaccine and vaccine access problems.(12, 14-21) Conversely, children are more likely to receive the influenza vaccine if their parents recall the child's specialist recommending it, have adequate awareness and knowledge, believe that the vaccine is effective, safe and easy to access, and if their children are younger in age (<6 years), have previously had influenza vaccine, have more than one SRMC, and that their parents or relatives believe it is necessary along with positive social influences.(11, 13, 15, 18-20, 22, 23)

Interventions to improve influenza immunisation coverage rates

Data informing ways to overcome barriers to vaccine receipt are limited. A systematic review comprising 25 studies assessing strategies to improve influenza immunisation in children with SRMC found that interventions targeting practices, and parent or patients increased coverage by 15% (95%CI: 13-17%) and 57% (52-61%) respectively.(24) However, most studies were conducted in the United States of America (USA), focused only on children with asthma and utilised traditional reminder/recall systems (e.g., written correspondence and telephone calls) that are financially costly, difficult to track receipt and labour intensive to administer. Text-message reminders sent by immunisation providers are a low-cost alternative and have been shown to increase vaccine uptake in some increased-risk groups.(25-28)

Notably no studies have investigated the impact of electronic reminders on influenza immunisation coverage in children with SRMC.

Approach to promoting influenza immunisation in children with SRMC

Despite a recommended and funded program targeting children with SRMC, Australia lacks a coordinated implementation-coverage feedback loop, similar to other countries globally.(29, 30) While some hospitals have established services providing immunisation free of charge to children with SRMC, many hospitals and providers recommend that children attend their GP for immunisation, adding to the burden of healthcare visits these families require. Research demonstrates that parents who receive a recommendation from their paediatrician or specialist are up to 16 times more likely to immunise their child.(11, 13) However, less than 58% of parents recall their child's paediatrician recommending influenza immunisation when asked at the end of the season or the following year.(11, 13) Current influenza immunisation protocols often lack consultation with providers and parents and vary significantly, even between departments within the same hospital.(31)

Multi-component interventions are optimal for improving immunisation coverage as they overcome many direct and indirect factors that affect the vaccine decision-making process to address multiple barriers simultaneously. Based in the USA, the Text4Health program implements and evaluates, using randomized control trials, tailored, targeted vaccine text message reminders, with a focus on influenza in urban paediatric and pregnant populations.(27, 28, 32, 33) Other research targeted at the diverse and complex information needs of pregnant women (34, 35) and other special-risk groups (25, 26) demonstrate text-messaging interventions improve coverage. Barriers to influenza immunisation in children with SRMC include: i) a lack

of ready access to immunisation services; ii) a lack of healthcare provider recommendation; iii) providers advising against immunisation; iv) safety concerns; v) competing priorities; vi) a lack of understanding of the need to immunise and vii) being unaware of the recommendation to immunise. (11-13, 36) Several barriers also exist at the provider level with a sense of responsibility, knowledge and confidence of determining 'at risk' conditions, key drivers towards providing a recommendation.(31)

Flutext-4U intervention

The **Flutext-4U** intervention package includes three components which are centrally coordinated. At the tertiary-level: prompt/reminder stickers are placed on medical cases notes and bookmarks at the relevant clinical notes page for notes entry by the clinician to assist hospital specialists to facilitate vaccine recommendation; at the primary care-level: a hard copy communication letter is sent to the child's treating (referring) GP. The written correspondence will advise the GP of the quality improvement initiative to improve low rates of influenza in children with SRMCs and ask them to assist as part of the child's treating team to improve influenza vaccine uptake. The parent-level component includes a text message reminder sent to the child's parent (on behalf of the hospital) advising them that their child/adolescent is eligible for funded influenza vaccine and that they can receive it upon request at the WCH on-site immunisation clinic or at their GP.

Methods and analysis

Study design

This parallel-group randomised controlled trial will measure the impact of the Flutext-4U intervention on receipt of influenza vaccine in children with SRMC, who are patients attending specialist appointments at the Women's and Children's Hospital

(WCH), South Australia. Participants will be randomly allocated to one of two combinations of Flutext-4U components. Participants in study arm 1 (standard care) will receive the tertiary-level reminder prompts on medical case notes at outpatient appointments. Study arm 2 will comprise both the primary care and parent-level components, in addition to standard care (Figure 1).

The WCH is one of four public hospitals across metropolitan Adelaide providing care to children and adolescents aged < 18 years and is the state's leading provider of specialist care for children with acute and chronic conditions and the largest maternity and obstetric service. The WCH has 295 beds catering for all paediatric specialties and its Paediatric Emergency Department is a level 1 major trauma centre for children in South Australia. Each year, there are more than 30,000 admissions and about 5,000 births at the hospital. In addition, more than 250,000 people come to the hospital as outpatients.

The study has been approved by the Women's and Children's Health Network Human Research Ethics Committee (HREC/20/WCHN/5). The study will be conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines on Good Clinical Practice. Below, we describe the study protocol.

Primary objective

- Determine the difference in proportion of children and adolescents (aged > 6 months to <18 years) in intervention versus standard treatment arm receiving at least one dose of influenza vaccine by 30/09/2021 (the end of the trial period), with receipt defined as receipt of one or more doses of influenza vaccine,

confirmed on the Australian Immunisation Register (AIR) record (primary outcome) and parental report.

Secondary objectives

- Determine the difference between intervention and standard treatment arms in the proportion of children and adolescents receiving at least one dose of influenza vaccine during the optimal period (April 1 to June 30).
- Determine the difference between intervention and standard treatment arms in the time from randomisation to vaccination.
- Determine whether the impact of the intervention on the primary outcome is modified by the subgroups: i) age group (<5; 5-14, >14 to <18 years); ii) residential location (metro or regional according to the predefined postcodes for metro and regional areas of South Australia) and iii) paediatric subspecialty (diabetes, neurology, respiratory, gastroenterology, rheumatology, cardiology or other).
- Determine parental acceptability of the SMS intervention.

Procedures

Randomisation

Parents (of children/adolescents) will be randomised to study arm in a 1:1 ratio. The randomisation schedule will be prepared by an independent statistician (not otherwise involved in the conduct or analysis of the trial) using ralloc.ado version 3.7.6 in Stata version 16. Allocations will be performed using randomly permuted blocks, stratified by age-group (<5, 5-14, >14 to <18 years). The schedule will be provided electronically to the Women's and Children's Health Network (WCHN) ICT Applications System Support staff, who will allocate participants according to the randomisation schedule. The trial statistician will remain blinded.

Study processes

The Flutext-4U Study Coordinator will set up the system to deliver the specialist prompts (all study participants) and liaise with the WCHN ICT Applications System Support staff to set up text message reminders for parents and communication letters for GPs (trial arm #2) to be sent centrally from the WCH. Influenza vaccine signage will be placed around hospital.

Children with SRMC will be identified from the WCH's Outpatient Department's appointment lists and eligibility screening completed with paediatric specialists on a fortnightly basis, using criteria set out in the National Immunisation Program for funded influenza vaccination. A waiver of consent was approved for parents to participate in this trial. Children will be ineligible if they have already received the 2021 influenza vaccine prior to trial commencement (defined as receipt on AIR); are a younger sibling of another trial participant (to ensure parents are not randomised twice); have no listed mobile phone number for parent/ guardian; or have a diagnosis of Cystic Fibrosis, as these children already receive additional vaccine delivery support and influenza vaccine messaging within the WCH environment. Participants (parents) will be randomised to study arm and baseline demographic information will be collected for all parent-child pairs. Demographic data that may impact vaccine coverage will be collected and will include the child's age, gender, Aboriginal or Torres Strait Islander status, medical condition, postcode (to determine SEIFA and residential location, i.e., metro/regional) and previous influenza vaccine receipt in 2019 and 2020 (from AIR records).

Intervention components will be provided, as per study trial arm. Influenza vaccine reminder stickers and bookmarks will be placed on the hard copy paper medical

case notes of all study participants, this will occur once eligibility and enrolment are confirmed and will be up to two weeks but no less than one week prior to the appointment. As per study arm, a communication (letter) with the child's treating (referring) GP will advise them that the child is identified as qualifying for funded influenza vaccine and seeking them to assist as part of the child's treating team to improve vaccine uptake. Parental SMS text message reminders will be sent using 'Message Media' software in a non-directive educational approach automatically to the child's parent advising them that their child/adolescent is eligible for funded influenza and where they can receive it. These will be timed to be sent prior to and following scheduled WCH specialist appointments and will be sent up to two weeks but no less than one week prior to the appointment. Each child will receive a maximum of three SMS reminders, for appointments scheduled between the start of the seasonal influenza vaccination season and the end of July. The second SMS will be sent two weeks after the first SMS and the third SMS sent two weeks after the second SMS. The first child will be enrolled on April 15th, 2021. Text messages will cease if a parent replies to advise that the child is immunised and this is confirmed on the AIR. Text messages will comprise: i) the influenza vaccination message reminder text, ii) an option to reply if the vaccine has been received elsewhere. Parents will be encouraged to engage with their child's specialist, GP or immunisation provider to answer any related questions arising from the influenza vaccination message. Parents may opt-out of further text messages at any time.

At conclusion of the trial, parents in both trial arms will receive an SMS, to ask if the child had received an influenza vaccine in 2021. All collected identifiable data will be securely stored on a database held by the WCHN, with access to the database

controlled by password protection. Any data presented will be de-identified prior to presentation.

Patient and public involvement

Patient and public involvement will include influenza vaccine signage designed in conjunction with the Flutext-4U Expert Advisory Group and WCH Consumer Advisory Committee. Parents in both trial arms will receive a parental acceptability survey. Study results will be communicated to key stakeholders and findings will also be disseminated in peer reviewed scientific journals and presented at national and international conferences.

Study monitoring and surveillance

Flutext-4U is a behavioural intervention and as such there are no risks or harms associated with drugs, procedures or devices in this study. The assessment of known potential risks and benefits of the intervention indicate negligible risk through participation in this study. Any risk of psychosocial distress associated with receiving a vaccine communication (SMS/letter/ reminder) or discussing vaccines is unlikely and is outweighed by the anticipated benefits to the individual and or knowledge that might reasonably be expected from the results. The risk of the intervention is comparable to standard care. A risk assessment and management plan has been developed for all stages of the trial from trial design through to reporting and reflective of the nature of the trial as behavioural intervention. A Trial Management Group comprising the chief investigator, project manager and study coordinator and statistician will closely review all operational aspects of the conduct and progress of the trial and a Trial Steering Committee comprising the investigator team and specialist paediatricians from the study institution, will maintain clinical and ethical oversight.

Sample size and analysis plan

We plan to enrol at least 540 parents of children / adolescents medically at-risk receiving tertiary care at the WCH. In order to have 80% power to detect a 30% relative increase in the percentage of children vaccinated from 40% in the standard care arm to 52% in the trial arm containing all Flutext-4U components, a sample size of 270 children per group is required (two-tailed alpha = 0.05). Previous studies have shown a 30% to 70% relative increase following other immunisation interventions. A 30% relative increase in the percentage vaccinated would be considered clinically meaningful.

All analyses will be undertaken on an intention-to-treat basis according to a statistical analysis plan, pre-specified prior to database lock. For the primary outcome, the number and proportion of participants receiving influenza vaccination in each group will be compared between randomised groups using logistic regression, with adjustment made for age-group (<5, 5-14, >14 years). The effect of treatment will be described using an odds ratio with a 95% confidence interval. Subgroup analysis will examine the effect of paediatric subspecialty (diabetes, neurology, respiratory, gastroenterology, rheumatology, cardiology or other), age group (<5, 5-14, >14 to <18 years) and residential location (metropolitan, rural according to the predefined postcodes for metro and regional areas of South Australia) on the primary outcome. Secondary analyses will be performed using logistic regression for binary outcomes and a Cox proportional hazards model for time to event outcomes, again with adjustment for age group (<5, 5-14, >14 to <18 years). In all analyses, a two-sided p-value < 0.05 will be used to indicate statistical significance. No adjustment will be made for multiple pre-planned comparisons, as the overall comparison of vaccine

uptake is of primary interest. The study statistician undertaking analysis will remain blinded to trial intervention assignment.

Discussion

This study will assess the effectiveness of a structured multimodal strategy using evidence-based tools and targeting a paediatric hospital and parents of children with SRMC to increase child influenza immunisation coverage rates. The intervention combines primary care-level and parent-level interventions and was designed for delivery in conjunction with a tertiary-level environment.

Improving immunisation coverage in high-risk populations remains at the forefront of implementation research. Yet, investment into programs and research to ensure funded vaccines are administered to those who need them most has been limited. Only 43.9% (WCH) children with SRMC received influenza vaccine in 2015, despite a funded influenza program for this at-risk group.(11)

Many modifiable barriers to annual influenza immunisation exist and multimodal strategies using: i) practice-level or ii) patient (or parent)-level interventions have been shown to improve immunisation rates. Employing extensive pilot data obtained by our research from parents and healthcare workers we are uniquely placed to develop, implement and evaluate Flutext-4U. Flutext-4U is a structured multimodal strategy using evidence-based tools and targeting paediatric hospitals and parents of children with SRMC to increase child influenza immunisation coverage rates. Flutext-4U will be implemented at the WCH using a randomised controlled trial design followed by thorough evaluation.

We are mindful of the inherent risk from contamination from intervention arm participants, particularly within medical risk groups due to parent interaction. To

minimise bias at the tertiary provider level and because randomising sub-specialists would be impractical, with an almost certain chance of cross-contamination, both intervention arms will receive standard care.

It is also important to collect data on parental acceptability of the intervention as this will have the potential to inform any adaptations to the future implementation of the intervention. Flutext-4U will develop coordinated approaches to immunising children with SRMC and establish the evidence required to optimise paediatric influenza immunisation strategies and campaigns. It will provide a model for future targeted high-risk programs nationally.

If the study demonstrates no negative effects, the intervention will be subsequently implemented for all children with SRMC at the WCH. Any impact on coverage will assist other Australian jurisdictions and national program directors in the implementation of similar programs. Additionally, a focus on developing low-cost, adaptable and scalable methods for improving coverage rates is expected to have implications for many at-risk populations so that the intervention could be adapted and tested in other populations.

Ethics and dissemination

The protocol and all study materials have been reviewed and approved by the Women's and Children's Health Network Human Research Ethics Committee (HREC/20/WCHN/5). The trial will be conducted in compliance with the current version of the protocol. Any change to the protocol document that affects the scientific intent, trial design, participant safety, or may affect a participants willingness to continue participation in the trial is considered an amendment, and will

be submitted to the HREC, for approval prior to being implemented. Following completion of the trial, the results will be disseminated via peer reviewed publication and at scientific meetings, professional and public forums. The results will be disseminated regardless of the magnitude or direction of effect.

Authorship will be allocated using the guidelines for authorship defined by the International Committees of Medical Journal Editors and the role of each author will be published in line with journal requirements. There are no plans for the use of professional writers.

Authors' contributions

JT wrote the first draft with assistance from KH, TRS and HM. JF, JC, NS, AT, AK, RC, MF, LF, MD and CB contributed to the manuscript and all authors approved the final version for publication.

Competing interests statement.

JT is an investigator on a project grant sponsored by Industry. Her institution has received funding from Industry (GSK) for investigator led research. She does not receive any personal payments from Industry. HM is an investigator on clinical vaccine trials sponsored by Industry (Pfizer, GSK). Her institution receives funding

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Figure 1: Study design

Footnote: SRMC: special risk medical condition.

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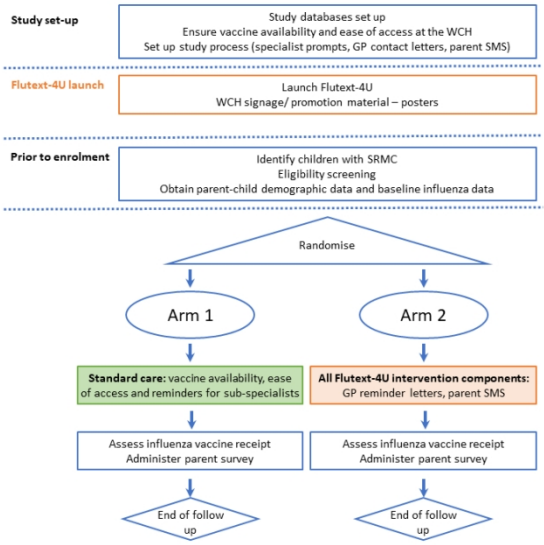

Figure 1: Study design

338x190mm (96 x 96 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Location in manuscript (page number)
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	Yes (available in trial register ACTRN12621000463875)
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	N/A
	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	N/A
	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)	14
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	3 & 6
	6b	Explanation for choice of comparators	8 &9
Objectives	7	Specific objectives or hypotheses	10
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)	9
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	9+10
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)	12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13
	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)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, 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	10/11

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)	12/13
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	14/15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
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	11
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	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11 &14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14
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	12/13

	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	n/a
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	13/15
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	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	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)	15
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	n/a
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	10
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	4 &10
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)	17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
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	
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	n/a
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	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17/18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Provided as supplementary material

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" license.