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Planned dose reduction of ocrelizumab in relapsing-remitting multiple sclerosis: a single-centre observational study

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ABSTRACT

Background Ocrelizumab, a humanised anti-CD20 monoclonal, is a highly effective treatment for relapsing-remitting multiple sclerosis (RRMS). The long-term safety of B-cell depletion in RRMS, however, is uncertain and there are no data on dose reduction of ocrelizumab as a risk mitigation strategy. This study aimed to evaluate the effectiveness and safety of reducing ocrelizumab dose from 600 to 300 mg in patients with RRMS.

Method Data were collected through the Townsville neurology service. Following the standard randomised controlled trial regimen of 600 mg every 6 months for 2 years, sequential patients consented to dose reduction to 300 mg every 6 months. Patients were included if they were diagnosed with RRMS and received at least one reduced dose of ocrelizumab. Relapse, disability progression, new MRI lesions, $CD19^+$ cell counts and immunoglobulin concentrations were analysed.

Results A total of 35 patients, treated with 177 full and 107 reduced doses, were included. The mean follow-up on reduced dose was 17 (1–31) months. We observed no relapses or new MRI activity in the cohort receiving the reduced dose, accompanied by persistent CD19+B cell depletion ($\leq 0.05\times10^9$/L). Mean IgG, IgA and IgM levels remained stable throughout the study. No new safety concerns arose.

Conclusions In this single-centre observational study, dose reduction of ocrelizumab from 600 to 300 mg every 6 months after 2 years appeared to maintain efficacy in terms of new inflammatory disease activity. A randomised trial may be warranted to confirm this and explore the impact of dose reduction on long-term safety.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Ocrelizumab has demonstrated high efficacy in relapsing-remitting multiple sclerosis (RRMS) but there are concerns regarding the safety of prolonged B-cell depletion. No prior data exist on reducing ocrelizumab dosage as a risk mitigation strategy in MS.

WHAT THIS STUDY ADDS

⇒ Reducing ocrelizumab from 600 to 300 mg in RRMS patients with stable disease after 2 years appears to maintain efficacy and CD19+B cell depletion persisted, suggesting this may be a potential risk mitigation strategy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study proposes reducing ocrelizumab dosage as a feasible risk mitigation approach in RRMS treatment. Larger trials are needed to confirm results and thoroughly assess long-term safety and efficacy. The reduced dose regimen has potential safety, practical and health economic benefits.

INTRODUCTION

Multiple sclerosis (MS) is a chronic neurodegenerative disease of the central nervous system (CNS), characterised by inflammation, demyelination, neuroaxonal loss and astrocytic gliosis.[1] It poses a significant burden on young adults, impacting their functional abilities, financial well-being and overall quality of life.[1] With a prevalence ranging from 50 to 300 per 100 000 individuals, MS affects approximately 2.3 million people worldwide, and its incidence continues to rise, leading to substantial socioeconomic implications.[2 3] While the precise aetiology of MS remains elusive, current research highlights the intricate interplay between genetic predisposition and environmental factors, including low serum levels of vitamin D, smoking, childhood obesity and Epstein-Barr virus infection.[1]

The clinical presentation and course of MS exhibit considerable heterogeneity, featuring substantial variability in neurological signs and symptoms. The National Multiple Sclerosis Society Advisory Committee has defined four primary phenotypes: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS) and progressive relapsing MS (PRMS).[4] At onset,

RRMS is the most common phenotype, accounting for about 85% of patients.[5]

Current strategies for managing MS can be broadly categorised into three areas: addressing acute relapses, alleviating neurological symptoms and reducing long-term inflammatory activity through disease-modifying therapies (DMTs).[3] Recent years have witnessed substantial advancements in both the number and efficacy of available DMTs, with over 20 medications undergoing clinical trials and real-world studies.[6] Of particular interest among these therapies are the anti-CD20 monoclonal antibodies; ocrelizumab, rituximab and ofatumumab.[7]

Ocrelizumab, the first anti-CD20 monoclonal antibody to be approved, is administered at a dose of 600 mg intravenously every 6 months for the treatment of both RRMS and PPMS.[7] This approval was granted following positive results from a phase 2 study and two large phase 3 trials in RRMS, where 600 mg of ocrelizumab every 6 months was compared with interferon beta-1a at 44 µg three times weekly.[8 9] Other anti-CD20 monoclonal antibodies, including rituximab and ofatumumab, have demonstrated similar effects. Notably, off-label use of rituximab has gained prominence in the treatment of MS and neuromyelitis optica spectrum disorders.[10] Additionally, ofatumumab recently gained approval in multiple countries based on results from the pivotal, randomised, double-blind, phase 3 ASCLEPIOS I and ASCLEPIOS II trials, which demonstrated its efficacy and tolerability in RRMS patients up to 30 months.[11]

While these therapies exhibit high efficacy, their prolonged use carries potential risks. Studies involving ocrelizumab and rituximab suggest that anti-CD20 monoclonal antibodies, by efficiently depleting memory B cells, exert long-term effects on inflammatory disease activity, potentially extending well beyond the licensed treatment interval. Despite generally good tolerance, continuous B cell depletion over 5–10 years may lead to hypogammaglobulinaemia, increasing the risk of infections and diminishing the effectiveness of vaccinations.[12] Consequently, it is relevant to investigate whether the efficacy of these treatments can be sustained and complications mitigated through various strategies, including personalised, extended interval or reduced dosing regimens.[13]

In the context of the ongoing COVID-19 pandemic, personalised and extended interval dosing of rituximab and ocrelizumab have emerged as potential risk mitigation strategies for RRMS patients, showing promising results.[13–16] However, there is a notable paucity of research on reduced dosing of anti-CD20 therapies. This study aims to address this gap by providing the first evidence regarding the feasibility of ocrelizumab dose reduction as a risk mitigation strategy for RRMS patients.

METHODS

Study design

This single-centre, retrospective, observational study was conducted through the Townsville neurology service to assess the effectiveness of dose reduction of ocrelizumab in patients with RRMS. Here, the standard treatment regimen of ocrelizumab consisted of a 600 mg intravenous infusion every 6 months for the initial 2 years, in accordance with the phase 3 OPERA trial protocol.[9] Subsequently, all sequential patients who had demonstrated stable disease course consented to a dose reduction strategy, which involved reducing the ocrelizumab dose to 300 mg every 6 months. A stable disease course was defined by no evidence of disease activity 3 criteria for a duration of 2 years, encompassing the combined absence of clinical relapses, radiological activity and disability worsening.[17]

All data for this study were collected as part of standard patient care procedures. Patients underwent clinical assessment every 6 months following the initiation of ocrelizumab to monitor for the occurrence of relapses or disease progression. Annual MRI scans were conducted to evaluate radiological activity. $CD19^+$ cell counts and immunoglobulin levels were measured before each ocrelizumab infusion during the dose reduction period.

Study population

A waiver of consent was granted to gain access to patients' health records under section 282 of the Public Health Act 2005 (the Act). Patients were included if they (1) were diagnosed with RRMS and (2) received at least one reduced dose of ocrelizumab by April 2023. Exclusion criteria were (1) diagnosis of PPMS, (2) diagnosis of SPMS within 12 months from the initiation of ocrelizumab treatment and (3) lack of follow-up data during the period of dose reduction. The classification of MS was based on the 2017 McDonald criteria.[18]

Study outcomes

The primary outcome was to investigate the clinical effectiveness of dose reduction of ocrelizumab. Clinical effectiveness was determined by the occurrence of new clinical relapse or radiological activity. Clinical relapse was defined as new or recurrent clinical episode with patient-reported symptoms and objective typical findings of MS, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection. Radiological activity was defined as the presence of T1 gadolinium-enhancing lesions at any time point or new/enlarging T2 lesions on the annual MRI.

The secondary objective of this study was to assess the laboratory effectiveness of ocrelizumab dose reduction. $CD19^+$ cells were chosen as a surrogate biomarker for B-cell depletion because the presence of anti-CD20 monoclonal antibodies can interfere with the flow cytometric analysis of $CD20^+$ cells.[19] In our investigation, we defined $CD19^+$ cell depletion as an absolute count falling below the lower limit of normal (LLN, 0.05×10^9/L) and $CD19^+$ cell repletion as a count equal to or above the LLN. Furthermore, we examined immunoglobulin levels,

Table 1 Baseline characteristics of the cohort

Characteristics	N=35
Age, years, mean (SD)	44.5 (10.9)
Female sex, n (%)	25 (71.4)
MS duration, years, median (IQR)	11.0 (7.0–16.5)
Patients with clinical relapses in the year before ocrelizumab infusion, n (%)	16 (47.1)
Patients with MRI activity in the year before ocrelizumab infusion, n (%)	18 (54.6)
Previous DMTs, n (%) ► None ► Interferons ► Glatiramer acetate ► Teriflunomide ► Dimethyl fumarate ► Natalizumab ► Fingolimod ► Alemtuzumab	13 (37.1) 3 (8.6) 2 (5.7) 2 (5.7) 1 (2.9) 5 (14.3) 2 (5.7) 7 (20.0)
Full doses, n	177
Reduced doses, n	107
Follow-up time total, months, mean (range)	20 (1–34)

DMTs, disease-modifying therapies; IQR, interquartile range; MRI, magnetic resonance imaging ; MS, multiple sclerosis; SD, standard deviation.

specifically IgG, IgM and IgA, due to existing evidence from clinical trials and observational studies suggesting a potential link between immunoglobulin levels and infection rates.[20] Hypogammaglobulinaemia was defined as having low immunoglobulin levels, with values falling below the LLN (5.76 g/L for IgG, 0.48 g/L for IgM, and 1.24 g/L for IgA). Conversely, immunoglobulin levels were considered normal if they met or exceeded the LLN threshold.

Data collection

Data were extracted from the patients' medical records, including age, sex, MS phenotype, date of disease onset, dates and doses of ocrelizumab infusions, $CD19^+$B cell counts and immunoglobulin levels. Clinical notes were reviewed to identify instances of relapses and MRI scans were examined for any evidence of radiological activity. The date of data censure was 30 April 2023. If a patient had progressed to SPMS, the year of transition was also recorded. If this had occurred within 1 year of ocrelizumab initiation, patients were excluded from further analyses. All patients were followed from the initial ocrelizumab infusion until either the date of data cut-off or the point at which they were lost to follow-up, whichever occurred first.

Data analysis

Data were grouped according to the number of dose reductions. Normally distributed data were summarised using means accompanied by SD. Non-normally distributed data were presented as medians along with IQRs. To assess the effects of ocrelizumab dose reduction on $CD19^+$ cell counts and immunoglobulin levels, we compared these figures to the LLN, using one-sample t-tests. A significance level of $p<0.05$ was established to determine statistical significance. Data management and statistical analyses were conducted using Microsoft Excel V.2016 (MS Excel 2016).

RESULTS

Study population

A total of 35 patients, treated with 177 full and 107 reduced doses of ocrelizumab, were included. The mean (SD) age of the participants was 44.5 (10.9) years, with 25 patients (71.4%) being female. At the time of ocrelizumab initiation, the median (IQR) disease duration was 11.0 (7.0–16.5) years with 47.1% patients with clinical relapses and 54.6% patients with MRI activity in the previous year. Patients remained under the dose reduction regimen for a mean duration of 20 months, ranging from 1 to 34 months. Seven patients were lost to follow-up before the date of data censure; one patient converted to SPMS, three experienced infections, one had difficulty with cannulation and two moved from the area. A summary of the main demographic and clinical characteristics of all patients is presented in table 1.

Primary outcome: clinical effectiveness

To assess the clinical effectiveness, we categorised the data based on the number of dose reductions within our study cohort. Among the 35 patients enrolled in the study, all underwent at least one dose reduction, with 28 receiving 2, 25 experiencing 3, 12 undergoing 4 and 8 receiving 5 by April 2023. We observed no clinical relapse or new MRI activity during the dose reduction period (table 2).

Secondary outcome: laboratory effectiveness

In evaluating the impact of ocrelizumab dose reduction on immunological parameters, we observed consistent trends. Most importantly, $CD19^+$ B-cells remained persistently depleted, with counts consistently below 0.05×10^9/L across multiple reduced doses of ocrelizumab (dose 1: $p<0.001$, dose 2: $p=0.001$, dose 3: $p<0.001$, dose 4: $p=0.01$, dose 5: $p=0.04$) (figure 1). Immunoglobulin levels, particularly IgG and IgA, also consistently remained above the LLN throughout the dose reduction period (figure 1). Notably, only IgA levels during dose 4 and dose 5 did not reach statistical significance ($p=0.07$ and $p=0.06$, respectively). Additionally, IgM levels demonstrated stability throughout the dose reduction phases, although statistical significance was not achieved.

DISCUSSION

In this single-centre observational study, we aimed to assess the impact of reducing ocrelizumab dosage from 600 mg to 300 mg every 6 months after 2 years of treatment in patients with RRMS. Our findings indicate that this dose reduction strategy effectively maintains efficacy in terms of controlling clinical relapses and radiological

Table 2 Mean and SD of clinical relapses and MRI changes

		Dose 1 (N=35)	Dose 2 (N=28)	Dose 3 (N=25)	Dose 4 (N=12)	Dose 5 (N=8)
Clinical relapses	n	35	28	25	12	8
	Mean (SD)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
MRI changes	n	13	10	7	7	1
	Mean (SD)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

MRI, magnetic resonance imaging ; SD, standard deviation.

disease activity out to almost 3 years postdose reduction. Notably, serum markers, including $CD19^+$ B-cell levels and immunoglobulin concentrations, remained stable under this modified regimen.

Our real-world data confirm the low clinical and radiological activity observed in RRMS patients treated with ocrelizumab. This is consistent with the results of the open-label extension (OLE) of the OPERA trials, which assessed the long-term effectiveness of ocrelizumab. In the OLE study, therapeutic benefits of ocrelizumab at the dose of 600 mg were maintained over 7.5 study years of follow-up with the adjusted annualised relapse rate of 0.03 and a near complete suppression of MRI disease activity.[21]

However, the available evidence on the practice of dose reduction for anti-CD20 therapies remains notably limited. To date, only two studies have explored this area, primarily focusing on rituximab. In a prospective observational cohort comprising 57 patients with RRMS and SPMS, the de-escalation of rituximab dosage from 1000 to 500 mg every 6 months did not result in a recurrence of disease activity during a 12-month follow-up period.[22] Similarly, a recent retrospective cohort study found that low-dose rituximab administration, specifically less than 1000 mg yearly, effectively suppressed inflammatory disease activity.[23]

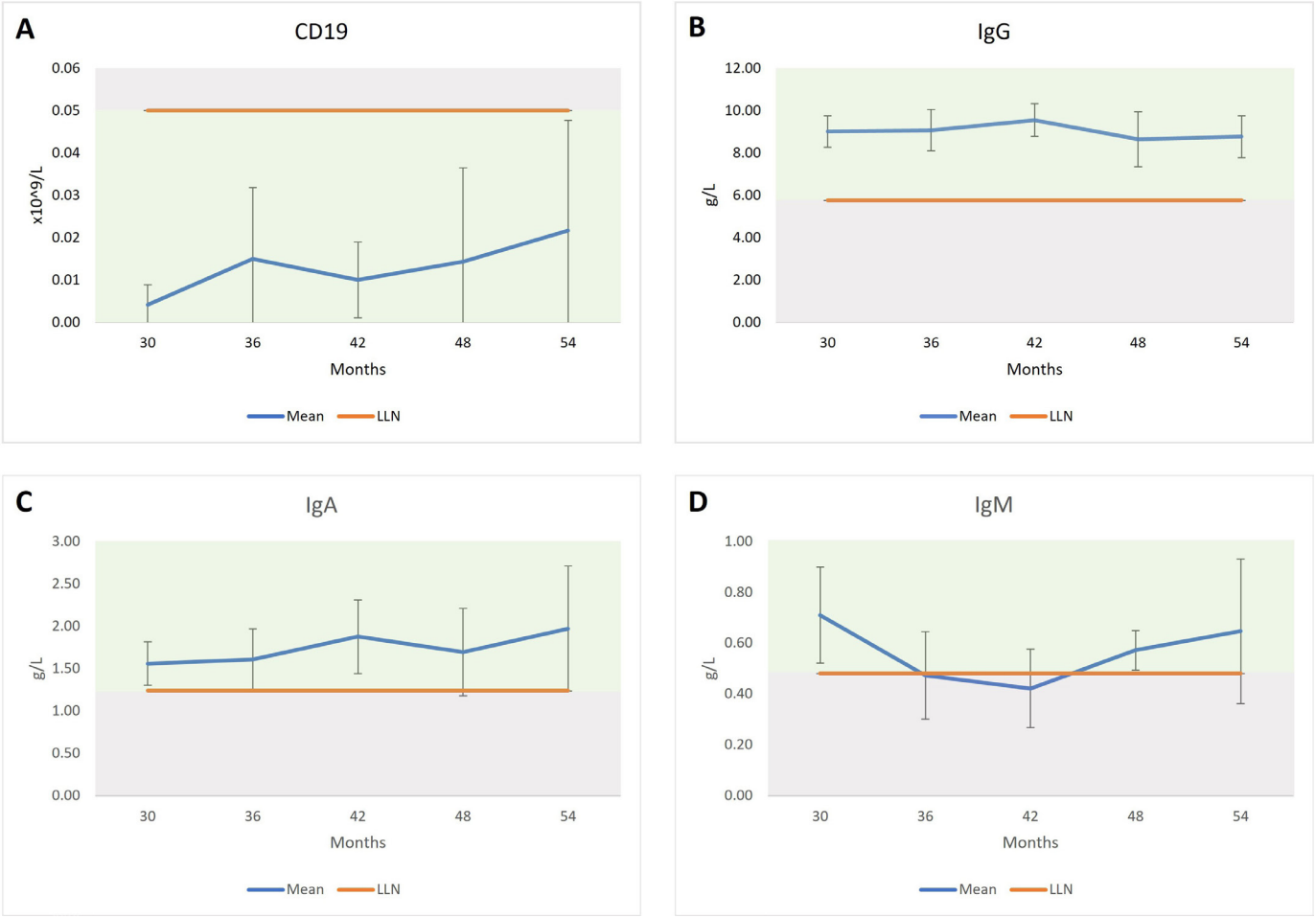

Figure 1 Comparison of CD19, IgG, IgA and IgM levels with LLN. (A) $CD19^+$ B cell count. (B) IgG cell level. (C) IgA cell level. (D) IgM cell level. Green shade denotes favourable zones; grey shade denotes unfavourable zones. LLN, lower limit of normal.

This study expands on this knowledge base by providing the first evidence suggesting the efficacy of low-dose ocrelizumab in RRMS both clinically and biologically. Mean $CD19^+$ B-cell counts remained persistently below the LLN throughout the study period. This stands in contrast to other dose-related risk mitigation strategies, notably extended interval dosing, where $CD19^+$ B-cell repopulation was observed in as many as 94% of patients.[15 24–27] According to a study by Gibiansky *et al*, the dosing interval of 6 months is important to ensure continuous depletion of peripheral blood B cells throughout treatment.[28] While the results are favourable for a dose reduction regimen, it is essential to acknowledge that, currently, there exists no concrete evidence suggesting a direct association between B-cell repopulation and clinical outcomes in the context of MS.[28] Future research should aim to investigate the intricate relationship between different dosages and intervals of ocrelizumab administration, B-cell repletion rates and their impact on clinical outcomes.

In terms of safety, long-term B-cell depletion resulting from ocrelizumab use has been linked to an elevated risk of hypogammaglobulinaemia and severe infections.[29] While our study did not specifically collect data on adverse events, it is noteworthy that three patients discontinued treatment due to infections. This appears slightly higher than the rate of infections reported in a safety analysis encompassing 11 clinical trials conducted over a span of up to 7 years (2.01 per 100 annually).[29] It is possible that this difference may be influenced by data collection over the COVID-19 pandemic, where cases of prolonged infection have been documented in individuals with B-cell immunodeficiency.[30 31]

Additionally, immunoglobulin levels remained consistently above the LLN during this treatment regimen, out to almost 6 years from drug initiation. In comparison, data from the OLE of the OPERA trials showed a gradual decline in serum IgG levels at an average rate of −0.33 g/L per year, with a significant drop observed after the fifth cycle of ocrelizumab, as well as a steady decrease in IgM levels over time.[29] Moreover, real-world data from an Australian cohort receiving ocrelizumab treatment revealed that 2.3% and 9.3% of MS patients experienced IgG and IgM levels below the LLN after an average of 4.6 ocrelizumab doses.[32] Hence, our findings suggest that dose reduction of ocrelizumab may reduce or prevent this decline in immunoglobulin levels. However, cautious interpretation is warranted due to the small numbers in our study and the limited evidence regarding the association between B cell populations, immunoglobulin levels and infection risk in the literature; with peripheral B cells representing only a small proportion of the total B cell pool.[20]

The study is not without limitations. First, the real-world nature of the study introduced challenges related to variability in the structure of data collection and incomplete data coverage. These challenges may have resulted in the potential underestimation of radiological activity since not all patients underwent regular scans, and some were not imaged at all (severe claustrophobia in one case). Furthermore, the inconsistent acquisition of Expanded Disability Status Scale data in clinical practice prevented us from reliably assessing disability progression, making it difficult to determine the longer-term consequences of dose reduction on disability outcomes. Second, the retrospective observational design of the study made it susceptible to various forms of bias. For instance, confounding bias, which occurs when an unmeasured variable influences both the independent and dependent variables, may compromise the internal validity of the findings while selection bias, which arises from the non-random selection of study participants, may compromise external validity. In combination with the lack of a comparator arm, the relatively small sample size and the short follow-up duration, these biases present challenges to the robustness and generalisability of the results, constraining our ability to derive a definitive conclusion about the efficacy of reduced dose ocrelizumab in RRMS patients. Given these limitations, there is a clear need for a randomised trial to confirm our findings and provide a more comprehensive assessment of the impact of dose reduction on long-term safety and efficacy.

CONCLUSION

In summary, our study has generated evidence supporting the potential for dose reduction of ocrelizumab in patients with RRMS as a risk mitigation strategy. Considering the natural progression of MS, characterised by heightened inflammatory activity in the early stages that tends to diminish with age and disease duration, our findings suggest that initiating full dose ocrelizumab treatment at disease onset, alongside a gradual reduction in treatment intensity, may emerge as a preferred treatment strategy. This approach not only demonstrates promise in maintaining clinical and radiological stability but also effectively addresses key considerations in MS treatment. It has the potential to mitigate the risk of serious infections associated with prolonged ocrelizumab use, reduce the significant costs of this MS medication for patients and providers and reduce pressure on infusion units. Nevertheless, recognising inherent challenges and limitations, further exploration through larger trials is imperative to validate and comprehensively evaluate the long-term safety and efficacy of this strategy.

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Contributors MB conceived of the presented idea. TDQT, MB, LH, CH and NH contributed to the study design. TDQT, MB and SE collected data with the assistance of Research Data Laboratory at Townsville University Hospital. TDQT performed the data analysis and interpretation under the supervision of MB, CH and LH. TDQT drafted the manuscript and prepared the figures. MB, LH, CH and NH revised the manuscript and provided critical feedback. All authors contributed to and approved the final version of the manuscript. MB was the guarantor of the study.

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Competing interests None Declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Townsville Hospital and Health Service Human Research Ethics Committee (Reference ID: HREC/QTHS/79611A). A waiver of consent was approved under the Public Health Act 2005 (Grant Number: PHA 79611) as per the National Statement section 2.3.10.

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