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ORIGINAL ARTICLE

Normative Heart-Rate Corrected Values for Repolarisation Length From Holter Recordings in Children and Adults

Kathryn E. Waddell-Smith, MBBS, PhD, FRACP [a,b,c], Alexandra A. Chaptynova [b], Jian Li, BSc, MBChB [a], Jackie R. Crawford, NZCS [a], Halina Hinds, BAS [c], Jonathan R. Skinner, MD, FHRS [a,b,c,*]

[a]Green Lane Paediatric and Congenital Cardiac Services, Starship Children's Hospital Auckland New Zealand
[b]The University of Auckland, Department of Child Health, Auckland, New Zealand
[c]Green Lane Cardiovascular Services, Auckland City Hospital, Auckland, New Zealand

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Background Normative values for heart-rate corrected repolarisation length are not available in children and are scarce in adults. We wished to define repeatability and normative values of Holter recording measurements of repolarisation length in healthy individuals using a commercially available system, and compare measurements with those from 12-lead electrocardiograms (ECGs).

Methods Twenty-four-hour (24-) Holter recordings were made on 99 Healthy volunteers: 52 children (7 months to 14 years) and 47 adults (≥15 yrs). Mean and peak values of QTc, and RTPc (R-wave to peak T-wave) were assessed. Bazett heart rate correction was employed for each measurement and only heart rates between 40 and 120 bpm were analysed. The end of the T-wave was defined from the zero-crossing point. QTc was also determined from 12-lead ECGs from the same population by manual measurement recording the longest QTc of leads 2 and V5. The tangent technique was used to define the end of the T-wave.

Results Interobserver repeatability: mean QTc ±15 ms (CI 3.5%), peak QTc ±25 ms (CI 4.5%), mean RTPc ±3 ms (CI 1%), peak RTPc ±44 ms (CI 11%). Mean values were very similar for <15 years and all females and were therefore amalgamated: mean (±2 SD); mean QTc 424 ms (394–454), mean RTPc 291ms (263–319). Values were lower in males ≥15 years; (mean QTc 408 ms (370–446), $p<0.01$; mean RTPc 274 ms (234–314), $p<0.01$. The highest mean QTc value was 467 ms in an adult female. QTc from 12-lead ECG: females <15 years 409 ms (384–434) males <15 years 408 ms (383–433), females ≥15 years 426 ms (401–451), males ≥15 years 385 ms (362–408).

Conclusions Holter measurements of mean QTc and RTPc are highly repeatable. Males ≥15 years have shorter mean repolarisation length over 24 hours than males <15 years and all females. Mean QTc Holter values were on average 15–17 ms longer than QTc from 12-lead ECGs except in females >15 years.

Keywords QT interval • Repolarisation • Holter monitor • Puberty • Gonadal hormones • Repeatability

Introduction

Long QT syndrome (LQTS) predisposes to malignant ventricular arrhythmias causing cardiac arrest, predominantly in the young [1]. Diagnosis can be challenging due to the variation in clinical expression [2] with significant overlap in QT intervals between affected and unaffected individuals [3,4] and difficulties in measuring QT intervals [5]. Risk

*Corresponding author at: Green Lane Paediatric and Congenital Cardiac Services, Starship Children's Hospital, Private Bag 92024, Auckland 1142, New Zealand. Tel.: +64 9 3074949; Fax: +64 9 6310785; Email: jskinner@adhb.govt.nz

Table 1 Demographics of normative cohort. Healthy males ≥15 yo were younger than healthy females ≥15 yo.

Total	Age range; mean age (SD)	Females					Males					P-value		
		Total	Age range; mean (SD)	Total females <15	Females age range (years), (SD)	Total females ≥15 yo	Females ≥15 yo age range (years), (SD)	Total	Age range, mean (SD)	Total males <15	Males <15 yo age range (years), (SD)	Total males ≥15 yo	Males ≥15 yo age range (years), (SD)	Females <15 yo vs males <15 yo	Females ≥15 yo vs males ≥15 yo	Females vs males
99	7 months–67 years; 19 (13)	49	7 months–67 years; 22.5 (16)	21	7 months–14 years; 7.5 (4)	28	20–67 years; 34 (11)	50	1–37 years, 15.4 (9)	31	1–14 years; 9 (3)	19	16–37 years; 26 (6)	0.12	0.006	0.007

Abbreviations: yo, years old.

stratification and allocation of appropriate therapy currently relies on either the manifestation of symptoms, which are often life threatening, or a corrected QT interval (QTc) exceeding 500 ms [1], which is frequently unrecognised by physicians [5]. Before these high risk features manifest, the young patient is exposed to a higher risk; unnecessary had they been identified at initial assessment. We wondered if Holter measurements might help identify genotype status or level of clinical risk but found that normative values are not available at all in children and are scarce in adults.

The use of Holter recordings in the assessment of LQTS has previously been studied with variable results. Some have demonstrated a higher proportion of pathological ventricular arrhythmias [6], and others not [7], although a longer QTc in LQTS subjects is commonly seen [3,7,8]. Some of these techniques appear to be complex and repeatability has not been established [8,9], and they have not been adopted widely.

We wished to trial a simplified Holter recording technique, using a commercially available system and software, to assess repolarisation length using the simple Bazett heart-rate correction formula, hoping this might be more readily adopted into clinical practice. The Bazett heart rate correction formula has been shown to work well across all heart rates, including in children [10], and commercially available Holter systems provide this calculation within their software. This software also permits the restriction of beats measured by heart rate. We decided to restrict the heart rates examined to between 40 and 120. The Bazett formula is less well validated for extreme bradycardia [11], and at faster heart rates clinical experience shows that defining the end of the T-wave can be difficult partly due to associated physical exertion or excitement often leading to movement artifact, and the T-wave may blend in with the subsequent p-wave [12], Furthermore, differentiation of genotype carrier state is improved at rates below 120 beats per minute (BPM) after exercise [13].

We thus aimed firstly to find the most repeatable measurement between QTc and RTPc (R-wave-to-peak-T-wave) for both peak and mean values, and then to establish normative upper and lower limits based on age and sex [14]. RTPc was selected as a potential alternative to QTc because the end of the T-wave can be challenging to determine precisely, and it is a measurement that is provided automatically by the company software. We also recorded 12-lead ECGs at the same visit to see how these QTc measurements compared with those from the Holter recordings.

Methods

This study was approved by the Health and Disability Ethics Committee New Zealand and local area health board: number: 16/NTB/86.

Study Population

Normative Holter recording data and 12-lead ECGs were obtained from healthy volunteers recruited through local

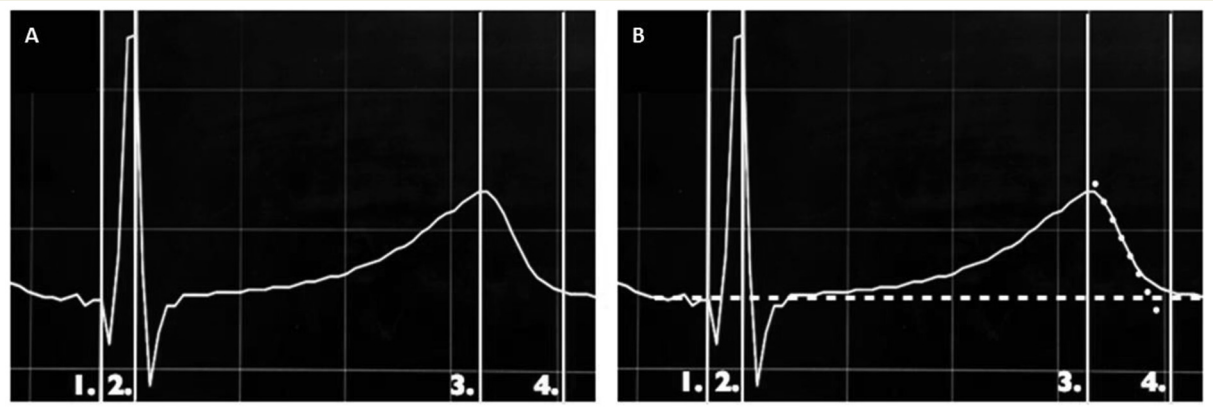

Figure 1 The QRS-T complex in lead CM 5 is used to determine measurements of repolarisation on the Holter monitor. Line "1." represents Q-onset, line "2." R-wave, line "3." peak of the T-wave and line "4." the end of the T-wave (zero crossing point). In Figure 1A, the lines generated by the Holter system are shown. In Figure 1B, the dotted lines demonstrate how the tangent technique would produce a shorter QT interval on this trace; this method was used on the 12-lead electrocardiograms (ECGs) because of its superior repeatability.

advertising within the hospital. Most were staff, or their relatives; all were unrelated to people with long QT syndrome. They were not taking QT prolonging medications; see Table 1 for Demographic Details.

Data Collection

ECG analysis

The first three authors (KWS, AC, JL) performed the 12-lead ECG analysis. None of the ECGs showed evidence of cardiac pathology. The QT interval was measured from the beginning of the QRS complex to the end of the T-wave as defined by the "tangent technique" where the tangent of the steepest slope of the second limb of the T-wave crosses the isoelectric line [15,16].

Holter recordings and analyses

All study subjects underwent a three-lead 24-hour Holter recording, and all heart beats of adequate quality within the restricted heart rate range were analysed from lead CM5 preferentially, or leads II or CM1 if the former was unavailable. LifeCard CF monitors and Del Mar Impresario software (Washington, USA) were used to calculate QT for heart rates between 40 and 120 beats per minute only. QT intervals of faster and slower rates were not recorded. This commercially available method uses semi-automated measurement, detecting the end of the T-wave as the zero crossing point using the Laguna algorithm [17] with caliper placement and periodic adjustment by the technician if the caliper obviously jumped from the appropriate position. This is uncommon, but tends to occur a few times over each 24 hours with baseline or movement artifact. Q-onset was defined as the onset of the negative deflection associated with the QRS complex, the R- and T-wave peaks were defined as the highest points in each in lead CM5 and end T-wave defined by zero crossing point at the baseline (Figure 1).

We anticipated that this method would tend to give a longer QT than the "tangent' technique but an algorithm for automated measurement using the tangent method was not available to us. Bazett correction was used to calculate QTc; this is incorporated in the computer software and gives an automated report.

R-wave to peak T-wave (RTP), was also recorded and corrected in the same way for heart rate (RTPc). The effect of puberty on ventricular repolarisation was examined by comparing results before age 11 and after age 15.

Repeatability (reproducibility) was tested between and within observers for mean and peak QTc and and RTPc. Twenty (20) of the Holter recordings were analysed twice in a blinded fashion to assess within-observer repeatability and a second physiologist scanned the same 20 recordings to assess between-observer repeatability.

Table 2 95% interobserver repeatability confidence limits for Holter recording measurements.

	95% interobserver repeatability limits (ms)	95% interobserver repeatability limits (%)
mQTc	±15ms	±3.5%
mRTPc	±3ms	±1%
peakQTc	±25ms	±4.5%
peakRTPc	±44ms	±11%

Statistical Analyses

Assumptions of the t-test were tested and all data were analysed by unpaired parametric and non-parametric t-tests as appropriate. Chi-squared tests were used for binary variables. Statistical analyses were performed using GraphPad

Table 3 Mean first ECG QTc, Holter mQTc and mRTPc values for healthy volunteers (21 females <15 years, 31 males <15 years, 28 females >15 years and 19 males >15 years). Mean (SD).

	Female <15 years	Male <15 years	All <15 years	All <15 years and Female ≥15 years	Female ≥15 years	Male ≥15 years	P-value Females <15 years vs Males <15 years	Female ≥15 years vs All <15 years	Male ≥15 years vs Female ≥15 years	Male ≥15 years vs All <15 years
First ECG QTc (ms)	409 (25)	408 (25)	408 (24)	411 (25)	426 (25)	385 (23)	0.94	0.07	0.01	0.04
Mean Holter mQTc (ms)	425 (16)	422 (13)	423 (14)	424 (15)	426 (18)	408 (19)	0.45	0.44	0.002	0.005
Mean Holter mRTPc (ms)	291 (15)	289 (11)	290 (13)	291 (14)	293 (16)	274 (20)	0.55	0.41	0.0007	<0.0001

ms=milliseconds.
Abbreviations: ECG, electrocardiogram.

Prism version 6.0e for Mac, (GraphPad Software, La Jolla, CA, USA, www.graphpad.com.)

Statistical analysis of observer repeatability tests was achieved through Bland Altman plots and 95% limits of repeatability. QTc, and RTPc intervals were compared using one-way Anova. These statistics were performed using SAS statistical package (version 8, SAS Institute, Cary, NC, USA). In all cases, two-tailed $p<0.05$ were considered statistically significant.

Results

Study Population

Normative ECG and Holter data were obtained from 99 healthy volunteers.

Repeatability of Holter Recording Assessment

Ninety-five per cent (95%) confidence limits for interobserver repeatability are reported in Table 2. Repeatability values for averaged measurements were remarkably good, particularly in comparison to previous reports of 12-lead ECG interpretation of QTc [5]. Measurement to the peak of the T-wave (i.e. RTPc) was more repeatable than to the end of the T-wave (i.e. QTc) (Table 2), and repeatability of mean measurements was superior to peak measurements, (Table 2).

Holter Findings of Healthy Volunteers

Mean Holter QTc and RTPc values (mQTc and mRTPc)

Given the better repeatability for mean values, we analysed these results to form normative values. We examined the results by age and gender, dividing the cohort into four groups: females <15 years, males <15 years, females ≥15 years and males ≥15 years. For both measurements, males ≥15 years had significantly shorter average values than the others females ≥15 years, females <15 years and males <15 years (Table 3 and Figure 2).

To examine the potential effect of gonadal hormones on these results, we re-performed the analyses excluding adolescents aged 11–15 years on the assumption that most individuals 10 years old or younger have not yet reached puberty, and that the maximal changes would have occurred by the age of 16. Females aged ≤10 years had a similar mean QTc compared with adult females ≥15 years (p=0.85). Males aged ≤10 years had a shorter mean QTc compared with males ≥15 years (p=0.004). There was no significant difference between mRTPc values for the younger versus older females (p=0.84), but males ≥15 years had shorter mRTPc values than males <10 years (p=0.005). Since excluding the peri-pubertal results made no material difference, all values were included in the generation of the mean and ranges for females and males.

Formation of normative values

Due to the similarities in results between females <15 years, males <15 years and females ≥15 years, these results could be amalgamated in the generation of normative values.

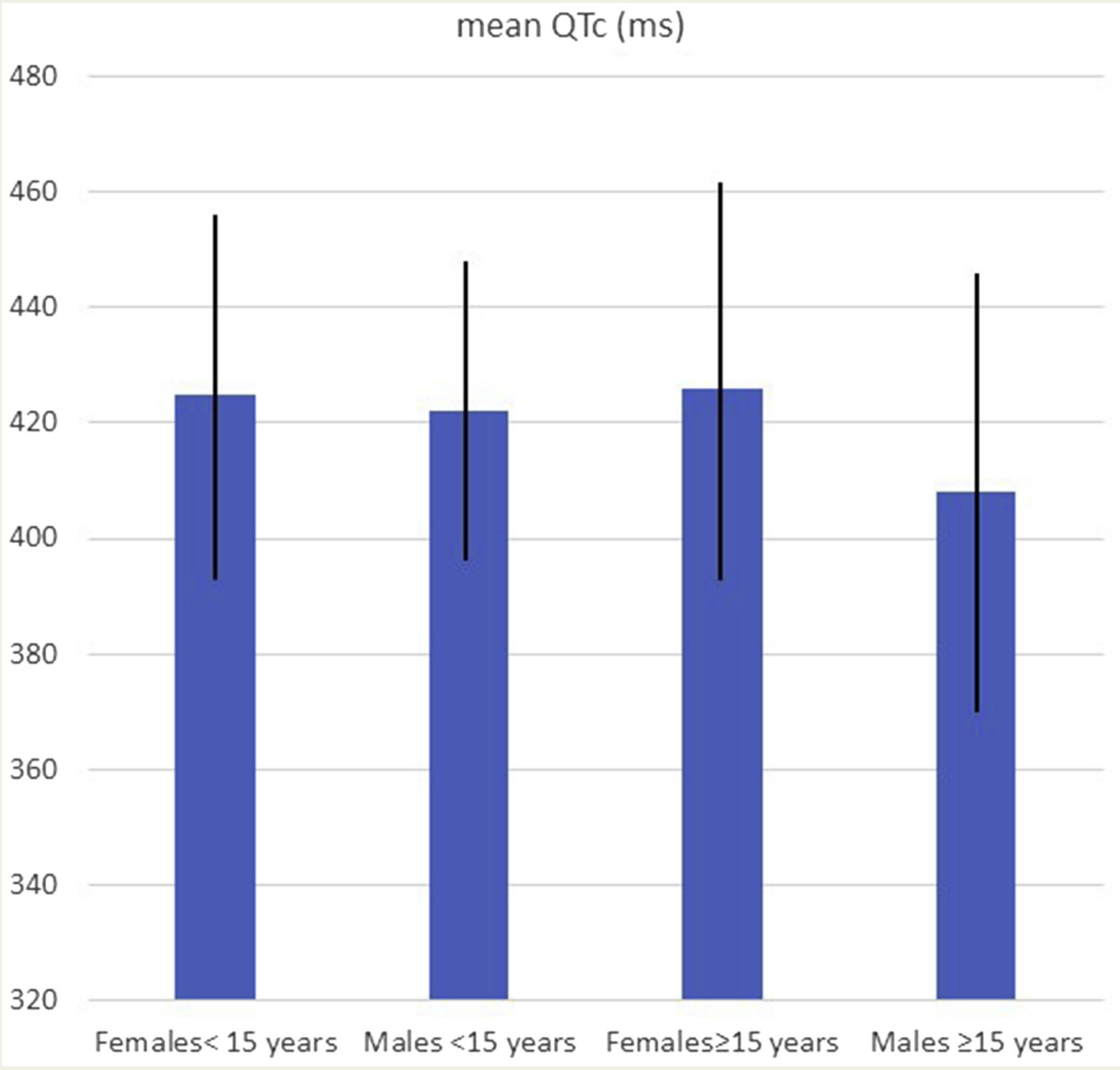

Figure 2 The mean QTc values from Holter recordings in 99 healthy volunteers with heart rates between 40 and 120 beats per minute analysed. Results are displayed in four age/gender subgroups. The height of the column shows the average mean QTc, and the bars show 2 standard deviations from the mean. The absolute values are shown in Table 2.

These values were significantly longer than for males ≥15 years, p=0.0002 (QTc) and p=0.0001 (RTPc) respectively. Therefore, we formed two reference ranges by expressing two standard deviations from the mean (i.e. including 95.5% of the population): (1) all females and males <15 years and (2) males ≥15 years (Table 4).

Discussion

This study finds that Holter recordings of repolarisation length are highly reproducible between observers. Mean values were more repeatable than peak values, and the most repeatable was mean RTPc (confidence intervals of 1%), followed by mean values for QTc (CI 3.5%), so these show the greatest promise for application into clinical practice. It is important to note that the mean QTc measurements were generally longer than those obtained from the 12-lead ECG. This may partly or entirely be related to the difference in how the end of the T-wave is determined by each technique, Holter determination of the end of the T-wave being determined from the zero-crossing point, compared to the tangent technique in the 12-lead ECGs.

A previous study of 21 healthy adults reported 95th centile values for mean QTc very similar to the upper limits we report here: they reported 439 ms in males versus 446 ms here, and 461 ms in females, versus 462 ms here [18]. Another study of 422 healthy adults observed differences in how QT interval changes against heart rate, producing nomograms of

Table 4 Mean Holter mQTc and mRTPc findings for each age/sex based normative group. The newly formed reference range is shown in bold in the third column.

	Mean value (SD)	Lower and upper limits (mean - 2SD and mean + 2SD)	Highest mean value recorded
mQTc all females and males <15years (ms)	424 (15)	**394-454**	467[a]
mQTc males ≥15years (ms)	408 (19)	**370-446**	436
mRTPc all females and males <15years (ms)	291 (14)	**263-319**	325[a]
mRTPc males ≥15years (ms)	274 (20)	**234-314**	303

ms=milliseconds.
[a]This value was recorded in an adult female.

QT against heart rate by gender; with women generally having longer QT intervals [19]. The authors also found that healthy people aged over 50 years have longer QT intervals. Heart rate corrected values, and average values, were not reported.

Repeatability of maximal values of repolarisation length was not as good, meaning that they are perhaps less likely to be of future clinical value. The confidence levels of repeatability are all very much less than those for manual QTc measurement from the 12-lead ECG found by other researchers [5]. This Holter technique may, therefore, prove to be especially attractive to non-LQT experts, for whom assessment of the 12-lead ECG is most challenging [5]. Furthermore, by including many hours of recordings we may be less likely by chance to miss a subject with long QT syndrome who has a normal QT interval for the few seconds the 12-lead ECG is obtained. Others have published that those with LQTS adapt poorly to changes in heart rate for example after exercise or standing [20,21], and we suspect that the Holter monitor takes advantage of this pathological process as a diagnostic tool. During a 24-hour Holter monitor period, there are many changes in heart rate, which can unmask the differences in repolarisation reserve between someone with LQTS and someone without.

A striking result was the lower overall QTc and RTPc in males ≥15 years compared to younger males and all females. This suggests that testosterone may, in healthy individuals, be a more powerful influence on QTc than the female sex hormones, confirming the conclusion of others from 27 years ago based on 12-lead ECG assessments [22]. In the practical sense, it means that the normative range is lower in males ≥15 years than all other groups. Larger numbers of males ≥15 years now need to be studied which will likely bring the normative upper limit down; for example the highest mean RTPc recorded in males ≥15 years was 303 ms, but the upper limit of normal derived from two standard deviations is 314 ms, due to the relatively small sample size. Another practical point to note is that almost 2.5% of the normal population will have values above the 2SD "normative" limits- and so a single value does not imply long QT syndrome is present—which has a prevalence of 0.05%. Such a measurement may raise suspicion along with other clinical features. Values from the long QT population need to be compared in future reports.

Mean RTPc had an even tighter repeatability than mean QTc (1% vs 3.5%). We consider this is most likely to be due to the automated detection algorithm for the end of the T-wave sometimes failing; the Laguna algorithm defines the zero crossing point. The cardiac technical staff often observed a jump of the caliper away from the T-wave, particularly when the end of the T-wave had a shallow slope or there was movement artifact or baseline wander. This was corrected when seen, but the algorithm detecting the peak of the T-wave was much more reliable. Whether this will be of clinical importance in the assessment of other types of long QT syndrome remains to be seen, given the variety of T-wave morphologies encountered.

The study has a number of weaknesses and limitations. The software did not allow us to use different heart rate correction formulae. We took a pragmatic approach to heart rate limitation at the outset (40–120 bpm), we cannot undo that and reanalyse all heart rates, which would be interesting for future studies, though recent work has suggested that the Bazett formula is in fact the best even for young children and infants with fast heart rates [10]. We have also not yet studied diurnal variation [9]. We also were not able to analyse changes in T-wave morphology, a science which has considerable promise.

Nevertheless, to our knowledge it is the first to report repeatability of a Holter technique to assess repolarisation and to produce age and sex based normative values for heart-rate corrected QT and RTP intervals, and may form the basis for research into factors influencing repolarisation length, such as genetic and pharmacological influences.

Conclusion

This study finds that a commercially available Holter recording system can provide highly repeatable assessment of repolarisation length and produces age and sex based normative mean values. A mean QTc of over 470 msec was not seen in healthy children or women, and a mean QTc over 450 msec was not seen in healthy males over 15 years of age. The study finds that males ≥15 years have shorter mean repolarisation length than women and children suggesting that testosterone rather than oestrogen or progesterone plays the dominant role in determining cardiac repolarisation length in healthy individuals.

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Conflicts of Interest

There authors have no conflicts of interest to declare.

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Ethics Approval

This study was approved by the Health and Disability Ethics Committee New Zealand and local area health board: number: 16/NTB/86.

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