

# Clinical outcome using a modified treat-and-extend protocol for neovascular age-related macular degeneration

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## ABSTRACT

**Aim** To compare outcome between patients treated using a modified treat-and-extend (mT&E) protocol and patients treated using a conventional T&E protocol.

**Methods** A retrospective cohort study of two groups of treatment-naïve neovascular age-related macular degeneration patients within a single centre were evaluated. One group treated using the conventional T&E protocol, with visual acuity, dilated fundus examination (DFE) and optical coherence tomography (OCT) performed at each visit. The second group treated using the mT&E protocol in which visual acuity and DFE were performed only every three visits. The main outcome measures were time spent per clinical visit, visual and anatomical outcomes measured for 36 months.

**Results** The T&E and mT&E groups included 135 eyes in 116 patients and 119 eyes in 94 patients, respectively, with similar baseline characteristics. At 36 months, the number of injections administered ( $7.9 \pm 2.9$  vs  $8.1 \pm 2.3$  injections, respectively;  $p=0.55$ ), the percentage of eyes that gained  $\geq 15$  Early Treatment for Diabetic Retinopathy Study (ETDRS) letters (23% vs 25.2%, respectively;  $p=0.39$ ) and the percentage of eyes that lost  $\geq 15$  ETDRS letters (21.5% vs 17.7%;  $p=0.43$ , respectively) were similar between the T&E and mT&E groups. However, waiting and contact time were reduced during the OCT-only visits compared with the full visits, with an average of 41 min saved per patient encounter.

**Conclusions** Both protocols yielded similar visual and anatomical outcomes. However, the mT&E protocol reduced the number of full visits, with considerably less time spent at the clinic.

## INTRODUCTION

Intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) compounds are an effective treatment for neovascular age-related macular degeneration (nvAMD).<sup>1–3</sup> Given the high global prevalence of AMD and other VEGF-dependent retinopathies, intravitreal anti-VEGF injections are currently the most common intraocular procedure performed worldwide,<sup>1–4</sup> and this trend is expected to increase in the coming years.<sup>5</sup> The need for repeated clinic visits to manage AMD not only places considerable strain on the healthcare system's resources and capacity,<sup>6</sup> but also demands a considerable

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ During clinic visits of neovascular age-related macular degeneration (nvAMD) patients treated using the treat-and-extend protocol, they could either receive intravitreal injections (IVI) of anti-vascular endothelial growth factor (anti-VEGF) only, IVI plus optical coherence tomography (OCT) or IVI plus a full assessment including dilated fundus examination. During full assessment visits, patients could spend up to 4 hours in the clinic, and health systems are overwhelmed by the increasing number of nvAMD patients.

## WHAT THIS STUDY ADDS

⇒ This study shows that there was a similar clinical outcome for two cohorts of patients; one receiving a full assessment plus IVI at every visit, and the other receiving IVI+OCT assessments in two of every three visits, and in one of every three visits or at least once in 6 months, they had a full assessment. During visits for IVI and OCT assessment only, the time spent in the clinic was reduced by more than half.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study indicates that omitting a dilated fundus examination and visual acuity assessment in two of every three clinic visits or performing a full assessment exam only once in 6 months, among nvAMD patients receiving IVI of anti-VEGF may not have visual or anatomic consequences. Reducing time spent during some clinic visits may increase adherence to treatment, alleviate the burden of nvAMD management on health systems, and improve clinic efficiency, without sacrificing clinical outcome.

commitment by these patients (the majority of whom are elderly) and their family members with respect to keeping their appointments.

In an attempt to reduce the burden associated with the high frequency of clinic visits needed to manage nvAMD, treatment protocols such as the treat-and-extend (T&E) regimen can reduce the number of clinic visits, while maintaining the safety and efficacy of standard fixed-monthly treatments. The T&E protocol provides patients with an individual treatment plan in which the



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interval between injections is adjusted based on the patient's clinical response.<sup>17</sup> Although the T&E protocol can reduce the total number of clinic visits and can yield excellent visual outcome,<sup>8,9</sup> it does not necessarily reduce the overall time that the patient spends at each visit, as it requires a full ophthalmic examination during each visit. In fact, in a recent study, the average visit time was 90 min and could be as long as 4 hours.<sup>10</sup>

The need to perform a dilated fundus exam (DFE) at every clinic visit was questioned previously in a post hoc review of patients in the HARBOR study, in which the authors noted that a DFE may not be needed for making subsequent treatment decisions during patient follow-up.<sup>11</sup> Likewise, Solomon *et al*<sup>12</sup> proposed that the interval between DFEs may be extended in order to reduce waiting time and increase patient satisfaction, without causing adverse events.<sup>12</sup>

Here, the aim is to evaluate the outcome of using a modified T&E (mT&E) protocol adapted in our clinic and compare to results obtained using the conventional T&E protocol.

## METHODS

### Study design

This retrospective study included two groups of consecutive patients with treatment-naïve nvAMD who began their anti-VEGF therapy at the Hadassah Medical Center, a tertiary referral centre. The patients in T&E group commenced treatment between January 2006 and December 2011, while the patients in the mT&E group commenced treatment between January 2016 and December 2017. Eyes that were treated with intravitreal injections of anti-VEGF compound for nvAMD and followed for 36 months were included. Exclusion criteria included previous photodynamic therapy, the presence of other retinal comorbidities, visually significant cataracts and previous ocular surgery other than uneventful cataract extraction. In bilateral cases, both eyes were included if both met the inclusion and exclusion criteria. The diagnosis of nvAMD was made in accordance to the Age-Related Eye Disease Study criteria and was based on ophthalmoscopy, optical coherence tomography (OCT) and fluorescein angiography findings.

### Data collection

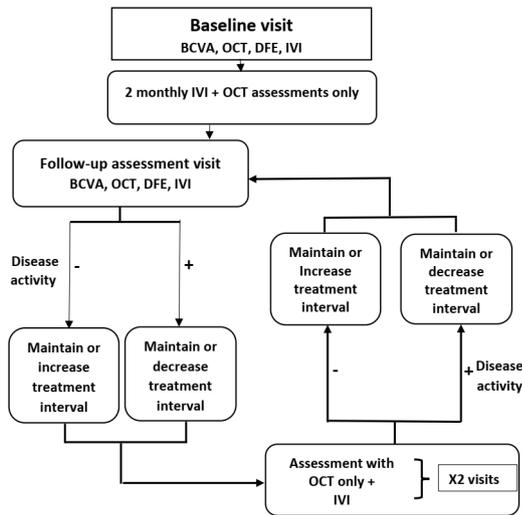
Demographics and clinical data were collected retrospectively from the patients' electronic medical records. Best-corrected visual acuity (BCVA) was routinely assessed using the Early Treatment for Diabetic Retinopathy Study (ETDRS) chart. The number, frequency and type of intravitreal injections administered were recorded. The OCT data were collected using a Stratus OCT (Carl Zeiss Meditec, Dublin, California, USA) or Spectralis HRA-OCT (Heidelberg Engineering, Heidelberg, Germany) prior to 2009 and from 2009 onward, respectively. To compare the Stratus OCT measurements with the Spectralis OCT measurements, a correction factor of 70 µm was added to the Spectralis OCT retinal thickness

values.<sup>13</sup> A researcher who was blinded with respect to the treatment protocol determined central point thickness (CPT, defined as the average of six radial scans at the foveola), central subfield thickness (CST, defined as the average thickness in the central 1 mm diameter) and the presence or absence of subretinal scars, subretinal fluid (SRF), intraretinal fluid (IRF), macular atrophy (as described previously,<sup>14</sup> and pigment epithelial detachment (PED) on OCT. Data from the Q-Flow platform (Q-nomy, Florida, USA), a virtual que management software, was used to evaluate the patients' time spent in the clinic. Using these data, we calculated the total waiting time (defined as the sum of time spent by the patient in the queue prior to performing the OCT scan, undergoing a full eye examination by the ophthalmologist, and receiving an intravitreal injection) and the total contact time (defined as the sum of time spent during the OCT scan, ophthalmic examination and intravitreal injection) during each full assessment visit and during each OCT-only assessment visit (where an ophthalmic exam was not performed) in the mT&E group.

### Anti-VEGF and treatment protocols

The T&E group were treated using the conventional T&E protocol.<sup>15</sup> In this protocol, BCVA, clinical examination and an OCT scan were performed at each visit and used to determine the subsequent treatment interval. Disease activity was defined as the presence of IRF, SRF and/or a new subretinal macular haemorrhage. Although no specific lower BCVA threshold for determining treatment has been established, treatment was generally withheld in eyes with BCVA poorer than 20/200 for which the treating physician believed that additional therapy would be futile. They were no other criteria for stopping anti-VEGF therapy. In both cohorts, the initial anti-VEGF treatment was bevacizumab. The anti-VEGF compound was switched from bevacizumab to either ranibizumab or aflibercept in cases in which IRF, SRF and/or sub-RPE fluid persisted or recurred despite ≥3 monthly injections with the previous compound. In both cohorts, extensions in treatment intervals were done in cases of disease stability or quiescence. These extensions were gradual of not more than 2 weeks at a time. However, in cases of disease activity, the treatment intervals could be shortened by more than 2 weeks at a time. In cases of bilateral disease, both eyes could be treated at the same time if they were due anti-VEGF therapy during the same visit. However, each eye, had its own treatment regimen, independent of that of the fellow eye, and if they had different treatment intervals, the visits per eye were followed independently.

The mT&E group followed the same injection regimen as the patients in the T&E protocol but received a full ophthalmic examination only once every 3–6 months; an OCT scan was performed at every visit. In the visits in which the patient was not examined by an ophthalmologist, the OCT scan was performed and evaluated prior to the intravitreal injection in order to determine the



**Figure 1** Flow chart depicting the mT&E algorithm. At the baseline visit, the patient undergoes a best-corrected visual acuity (BCVA), an optical coherence tomography (OCT) scan, a dilated fundus examination (DFE), and an intravitreal injection (IVI). At the next 2 monthly visits, the patient receives only an OCT scan and an IVI. Four weeks later, the patient then undergoes a full ophthalmic exam, an OCT scan, and receives an IVI; the treatment interval is then modified in accordance with the conventional T&E protocol. Subsequently, the patient receives an OCT scan and IVI every month, with a full ophthalmic exam performed every 3 months. mT&E, modified treat-and-extend; T&E, modified treat-and-extend.

interval until the next injection. In case of a new visual complaint, an ophthalmic examination was performed prior to the injection. The mT&E treatment algorithm is depicted in figure 1.

### Outcome measures

Outcomes included change from baseline BCVA, disease inactivity (defined as dry macula on OCT), change in CST and/or CPT from baseline, the number of intravitreal injections, and the average waiting and contact times spent during the visits.

### Patient and public involvement

Patient and public were not involved in anyway.

### Sample size calculation

Sample size calculated using formula for estimating differences in two independent samples with continuous outcome:

$$n_i = 2 \left( \frac{Z\sigma}{ES} \right)^2$$

where  $n_i$  is the sample size required for each group,  $Z$  is the value from the standard normal distribution reflecting the confidence level that will be used, and  $ES$  is the desired margin of error;  $\sigma$  reflects the SD of the outcome variable. In this case, the comparison was made using the average change in logMAR BCVA at 3 years. With  $Z=1.96$  for a 95% CI, the margin of error will be

0.15 logMAR BCVA. To obtain  $\sigma$  as a measure of dispersion, we used the data and SD from our previous study<sup>3</sup> in which the mean $\pm$ SD BCVA logMAR of patients at 3 years was  $0.496\pm 0.493$ . Thus,  $n_i = 2 \left( \frac{1.96 \times 0.493}{0.15} \right)^2 = 82.99$ . Therefore, a minimum sample size of 83 eyes in each group will ensure that the 95% CI for the difference in mean logMAR BCVA levels has a margin of error of no more than 0.15.

### Statistics

Statistical analyses were performed using SPSS, V.25.0 (IBM). After testing for normality, groups were compared using a paired Student's t-test or Wilcoxon signed-rank test, where appropriate. The prevalence of categorical parameters was compared using Fisher's exact test. Differences were considered significant at  $p < 0.05$ . Except where indicated otherwise, summary data are presented as  $n$  (%) or mean $\pm$ SD

## RESULTS

### Patient characteristics

The T&E cohort included 135 eyes from 116 patients; 41.4% of patients ( $n=48$ ) were female, and the mean patient age at the start of treatment was  $76.9\pm 7.8$  years. The mT&E cohort included 119 eyes from 94 patients; 55.3% of patients ( $n=52$ ) were female, and the mean age was  $79.8\pm 6.8$  years. Detailed demographic and clinical characteristics for both groups are summarised in online supplemental table 1. The percentage of patients with bilateral nvAMD was similar between the T&E and mT&E groups (16.4% vs 26.6%, respectively;  $p=0.09$ ). The number of injections performed per year was also similar between the T&E and mT&E groups ( $7.9\pm 2.9$  vs  $8.1\pm 2$ , respectively;  $p=0.55$ ). Finally, the percentage of cases that switched treatment from bevacizumab to either ranibizumab or aflibercept was similar between the T&E and mT&E groups (32.6% vs 31.1%, respectively).

### Time spent in the clinic

During a full assessment clinic visit, the mean total waiting time was  $56\pm 40$  min (range: 3–105 min), and the mean total contact time was  $26\pm 10$  min (range: 14–49 min). During an OCT and injection only visit, the mean total waiting time was  $32\pm 20$  min (range: 2–89 min;  $p < 0.001$  vs during full assessment clinic visit), and the mean total contact time was  $9\pm 4$  min (range: 6–17 min;  $p < 0.001$  vs during full assessment clinic visit). Thus, on average the patients who were treated using the mT&E protocol spent approximately 41 min less during the OCT and injection only visits than in a full assessment visit.

### Visual outcome

Baseline and final BCVA and anatomical outcomes are summarised in table 1. Mean baseline BCVA was similar between the T&E cohort ( $\sim 53$  ETDRS letters) and the mT&E cohort ( $\sim 50$  ETDRS letters). In the T&E cohort, a higher percentage of eyes had baseline BCVA of 0.5 logMAR (20/40) or better compared with the eyes in

**Table 1** Baseline and final (36-month) clinical characteristics in the T&E and mT&E groups

	Baseline		P value*	36 month follow-up		P value*
	T&E group (n=135 eyes)	mT&E group (n=119 eyes)		T&E group (n=135 eyes)	mT&E group (n=119 eyes)	
LogMAR BCVA	0.69±0.63	0.78±0.69	0.28	0.72±0.70	0.74±0.76	0.83
BCVA						
20/200 or worse	27 (22.7)	32 (23.7)	0.36	32 (26.9)	33 (24.4)	0.67
>20/200 to <20/40	47 (39.5)	68 (50.4)	0.10	35 (29.4)	52 (38.5)	0.15
20/40 or better	45 (37.8)	35 (25.9)	0.04	52 (43.7)	50 (37.1)	0.31
ETDRS letter ≥45	103 (86.6)	83 (61.5)	<0.001	99 (83.2)	83 (61.5)	<0.001
CPT, microns	408.7±183	370.8±192.7	1.00	326.7±204	273.3±116.5	0.05
CST, microns	414.7±145.7	390.4±119.7	1.00	349.1±166	307.5±106.9	0.04
IRF	64 (47.4)	53 (44.5)	0.71	44 (32.6)	37 (31.1)	0.89
SRF	80 (59.3)	72 (60.5)	0.90	38 (28.2)	26 (21.8)	0.31
PED	53 (39.3)	80 (67.2)	<0.001	47 (34.8)	72 (60.5)	<0.001
Scar	8 (5.9)	6 (5.0)	0.79	52 (38.5)	55 (46.2)	0.25
Atrophy	6 (4.4)	8 (6.7)	0.58	52 (38.5)	53 (44.5)	0.37

Data are presented as the mean±SD or n (%).  
 \*Calculated using Student's t-test or Fisher's exact test.  
 BCVA, best-corrected visual acuity; CPT, central point thickness; CST, central subfield thickness; ETDRS, Early Treatment for Diabetic Retinopathy Study; IRF, intraretinal fluid; mT&E, modified treat-and-extend; PED, pigment epithelial detachment; SRF, subretinal fluid; T&E, treat-and-extend.

the mT&E cohort (37.8% vs 25.9%, respectively,  $p=0.04$ ). At 12 months, BCVA was 56.2 and 53.6 ETDRS letters in the T&E and mT&E groups, respectively. At the final 36-month visit, BCVA was 52.9 and 51.9 ETDRS letters in the T&E and mT&E groups, respectively (similar to their corresponding baseline values).

The median change in BCVA over the 3-year follow-up period was similar between the T&E and mT&E groups (0.0 (IQR: -10 to 15) vs 0.0 (IQR: -5 to 15) ETDRS letters, respectively;  $p=0.91$ ). Considering eyes from bilateral cases only, the median change in BCVA over the 3-year follow-up period was also similar between the T&E and mT&E groups (0.0 (IQR: -6.3 to 5.0) vs 0.0 (IQR: -1.3 to 15) ETDRS letters, respectively;  $p=0.610$ ). **Figure 2A** shows the logMAR BCVA in both cohorts measured over 3 years of treatment, and **figure 2B** shows the percentage of eyes in each group that decreased by at least 15 ETDRS letters, increased by at least 15 ETDRS letters, or had a change that was  $\leq 14$  ETDRS letters (either decreased or increased) at various times points relative to baseline. As summarised in **table 2**, the change in BCVA at 3 years was similar between the two groups.

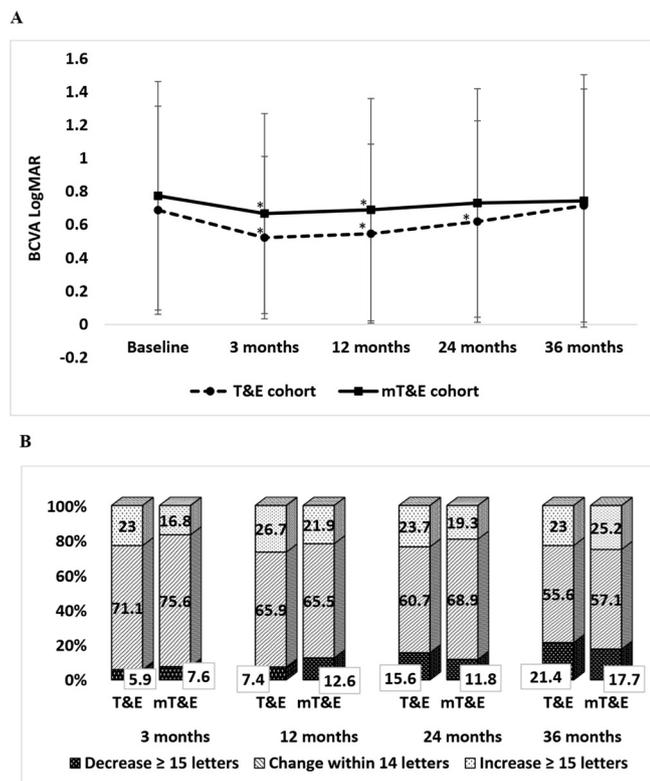
### Anatomical outcome

CPT and CST at baseline and during follow-up for both groups are shown in **figure 3A** and **figure 3B**, respectively. In both groups, both CPT and CST decreased significantly after the first 3 monthly injections and remained lower than their respective baseline values throughout the 36 months of follow-up. The median change in both

CPT and CST was similar between the T&E and mT&E groups. Except for PED, all other baseline and final clinical characteristics were similar between the two groups (**tables 1 and 2**). Considering eyes from bilateral cases only, the median change in CPT and CST were similar over 3 years ( $p=0.465$  and  $p=0.391$ , respectively).

### DISCUSSION

Here, we compared clinical outcome and visit duration between patients with nvAMD treated using a mT&E protocol versus the conventional T&E protocol. We found that although the patients in the mT&E group received a DFE and visual acuity (VA) assessment only once every three visits, they received the same number of intravitreal injections as the patients in the T&E group, who received the full ophthalmic examination and assessment at every visit. On average, omitting the VA assessment and DFE in two-thirds of the visits reduced the total visit duration by more than 50%. Trivizki *et al*<sup>16</sup> recently examined the putative benefits of using an OCT-guided retreatment model without assessing VA or DFE.<sup>16</sup> In their study, they dedicated 1 day in their clinic in which patients received only OCT-guided treatment, and they compared both the efficiency and cost-effectiveness of that approach to a standard model in which patients received a full ophthalmic assessment that included VA and DFE. The authors found that on the day in which patients received only OCT-guided treatment (and assuming that the office was sufficiently staffed), both efficiency and patient

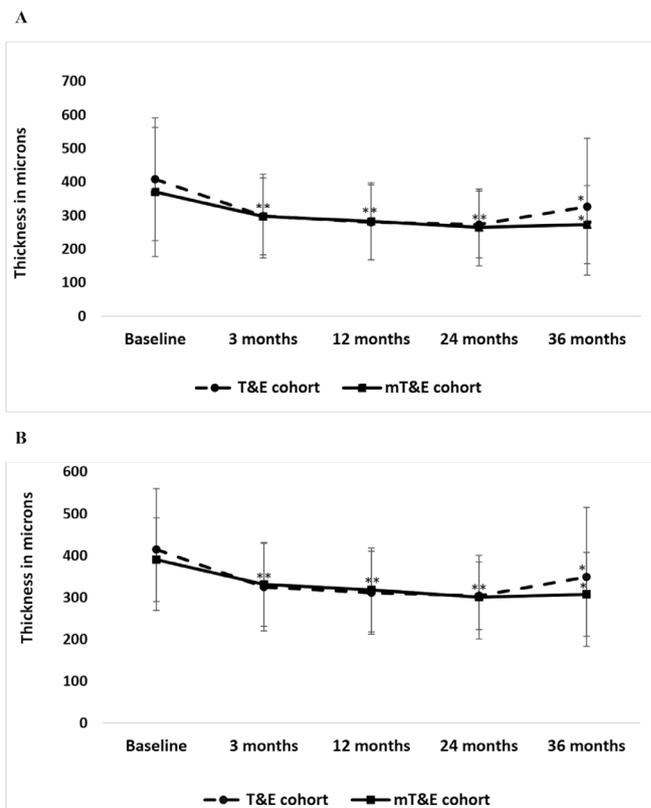


**Figure 2** Visual outcome was similar between the treat-and-extend (T&E) and modified T&E (mT&E) groups. (A) Mean logMAR best-corrected visual acuity (BCVA) measured in the T&E and mT&E groups at baseline and at the indicated follow-up times. \* $p < 0.05$  versus the corresponding baseline value. Error bars represent the SD. (B) Percentage of eyes in the T&E and mT&E groups with a decrease of  $\geq 15$  ETDRS letters, a change (either decrease or increase) of  $\leq 14$  ETDRS letters, and an increase of  $\geq 15$  ETDRS letters compared with the corresponding baseline. ETDRS, Early Treatment for Diabetic Retinopathy Study.

**Table 2** Summary of the change in clinical parameters in the T&E and mT&E groups between baseline and 36 months

	T&E group (n=135 eyes)	mT&E group (n=119 eyes)	P value*
Increase in BCVA of $\geq 15$ ETDRS letters, n (%)	31 (23)	30 (25.2)	0.39
Decrease in BCVA of $\geq 15$ ETDRS letters, n (%)	29 (21.5)	21 (17.7)	0.43
No of injections per year, mean $\pm$ SD	7.9 $\pm$ 2.9	8.1 $\pm$ 2.3	0.55
Change in CPT, median (IQR)	-106 (185.0)	-69.5 (133.3)	0.61
Change in CST, median (IQR)	-65 (136.5)	-56 (146.25)	0.55
No fluid at the final visit, n (%)	36 (26.7)	45 (37.8)	0.06

\*Calculated using Student's t-test, Wilcoxon signed-rank test or Fisher's exact test.  
BCVA, best-corrected visual acuity; CPT, central point thickness; CST, central subfield thickness; ETDRS, Early Treatment for Diabetic Retinopathy Study; mT&E, modified treat-and-extend; T&E, treat-and-extend.



**Figure 3** Anatomical outcome based on optical coherence tomography was similar between the T&E and mT&E groups. (A) Mean central point thickness measured in the T&E and mT&E groups at baseline at the indicated follow-up times. (B) Mean central subfield thickness measured in the T&E and mT&E groups at baseline and at the indicated follow-up times. \* $p < 0.05$  compared with the corresponding baseline. Error bars represent the SD. mT&E, modified treat-and-extend; T&E, modified treat-and-extend.

throughput increased, the cost per patient decreased, and clinic revenue increased.<sup>16</sup> However, it is important to note that the authors did not evaluate or compare clinical outcome between the two models. In addition, Das *et al*<sup>17</sup> recently reported that long waiting times during clinic visits are a contributing factor to non-adherence with medical appointments.<sup>17</sup>

In this study, we found that the T&E and mT&E groups were similar in terms of their baseline characteristics, and their visual and anatomical outcomes measured at 36 months were also similar. For example, VA improved in both groups after the first three injections, and this improvement was maintained for approximately 2 years in both groups, followed by a gradual decline in VA in both groups. This clinical course in terms of the change in VA in nvAMD during anti-VEGF therapy is similar to the course described extensively by several groups.<sup>2,3,15,18,19</sup>

An alternative modification of the conventional T&E protocol is the so-called observe-and-plan (O&P) protocol proposed by Mantel *et al*.<sup>20</sup> In this protocol, patients begin with three loading doses of intravitreal injections, followed by an observation period with monthly monitoring visits that help guide the injection interval based



on structural changes on OCT examination (eg, IRF and/or SRF) and/or DFE (eg, haemorrhage). Once the patient's time interval is determined, a fixed treatment plan is followed for a series of three injection visits, during which the patient receives the injections but is not assessed (ie, no BCVA or OCT assessment). After these three planned injection visits, the patient then undergoes a full assessment.<sup>20</sup> The O&P approach differs from our mT&E protocol in that we can modify the patient's treatment interval during the OCT-only visits. In addition, with the mT&E protocol the patient undergoes an OCT assessment at every visit, prior to receiving their injection; this is an important point, as a survey of ophthalmologists at the 2018 annual meeting of the American Society of Retinal Surgeons found that most decisions regarding re-treatment are based solely on OCT images.<sup>21</sup> In both the T&E and mT&E groups, the treatment intervals were only extended by 2 weeks at a time, according to the treatment protocol that had been adopted in the clinic, however, the possibility of extending treatment intervals by 4 weeks at a time were shown in the ALTAIR study,<sup>22</sup> and this was not evaluated in this study.

Despite its time-saving potential, our mT&E protocol may have some caveats that warrant discussion. For example, a valid argument against omitting full ophthalmic exams from two out every three visits is the potential risk of missing a macular haemorrhage that may not show as macular fluid detectable on an OCT scan. In their post hoc analysis of the HARBOR study, Patel *et al*<sup>11</sup> found that the prevalence of macular haemorrhage reduced from 89% at the baseline visit to 31% and 11% at 3 and 6 months, respectively.<sup>11</sup> Thus, the likelihood of macular haemorrhage decreases considerably following the start of anti-VEGF therapy. Moreover, the majority (89%) of macular haemorrhages are visible on spectral-domain OCT, and haemorrhages that are not visible on an OCT scan may not significantly affect the patient's VA outcome.<sup>11</sup>

An important addition when using the mT&E protocol is encouraging patients to self-assess and report any changes in their VA. For example, Mathew and Sivaprasad,<sup>23</sup> reported an increase in sensitivity and specificity (from 61% to 87.5% and 96.6% to 98.5%, respectively) after training their patients to identify and depict the distortion of objects and visual decline in their everyday environment; moreover, the patients' reported changes were correlated with clinical and morphological findings on OCT.<sup>23</sup>

Another possible concern associated with using the mT&E protocol is that by omitting the ophthalmic exam, the clinician may increase his/her risk of liability, given that missing a macular haemorrhage by omitting a DFE, may cause VA decline. To mitigate this risk, Trivizki *et al* proposed two measures.<sup>16</sup> First, they proposed that during an OCT-only visit the patient should always receive an intravitreal injection; thus, an injection should never be deferred based solely on OCT findings. Second, the follow-up interval should never be increased by more

than 2 weeks.<sup>16</sup> These two recommendations are consistent with our mT&E protocol. In addition, although a retinal tear following an intravitreal injection could be missed by omitting an ophthalmic exam, this complication is extremely rare, and the patient will usually experience visual complaints that prompt an ophthalmic examination.<sup>24</sup> Another potential complication is the possible development of high intraocular pressure (IOP) following an intravitreal injection; however, this is usually transient, typically returning to normal levels within 30 min in virtually all patients.<sup>25 26</sup> Nevertheless, although a sustained increase in IOP is rare, it can be an important complication, particularly among patients with preexisting glaucoma or risk factors for developing glaucoma<sup>27</sup>; these patients should therefore be monitored closely during the 3 monthly dosage injections in order to determine whether they are suitable to follow the mT&E protocol.

A major limitation of this study is its retrospective nature. Specifically, we were unable to assess the prevalence and possible consequences of missing a macular haemorrhage, retinal tear or increase in IOP. Nevertheless, the baseline clinical characteristics and overall visual and anatomical outcomes were similar between the T&E and mT&E groups. Another limitation is the difference in the recruitment periods of both groups (T&E group commenced treatment between 2006 and 2011, while modified T&E group was 2016–2017), given that knowledge, attitude and practices around disease conditions may vary overtime, both among patients and treating physicians. The time estimates were made using the Q-flow platform. The accuracy of the data from this platform also depends on the consistency and accuracy of the different staff members responsible for registering and moving patients from one service to another on the platform. Unfortunately, this was not often accurately done, and so the data were screened to include only clinic days with the most accurate and consistent data entry.

In conclusion, we found that treating patients with the mT&E protocol yielded similar visual and anatomical outcomes compared with treating patients using the conventional T&A protocol but reduced the number of full ophthalmic visits and considerably reducing the time spent at each visit. Thus, applying the mT&E protocol may help alleviate the often overwhelming—and increasing—burden placed on patients with nvAMD who are undergoing treatment with intravitreal injections. In addition, our results suggest that this protocol can increase the clinic's overall efficiency and patient throughput without sacrificing clinical care or outcome, ultimately increasing our patients' compliance with respect to following their treatment protocol. Finally, using the mT&E protocol can reduce waiting time in crowded facilities and will reduce contact time between patients and healthcare staff.

**Contributors** IC, YC and BNV contributed to study conception and design, YC and BNV did the data collection, analysis and drafting of initial manuscript. IC critically

reviewed and provided substantial intellectual content to the original manuscript. All authors read and approved the final version prior to submission and agree to be accountable for all aspect of the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. IC was the guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** The research protocol was approved by the Institutional Ethics Committee of the Hadassah Medical Center. Reference Number: 22-03.08.07. Consent waved by ethical committee.

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**Data availability statement** Data are available on reasonable request.

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