National Electronic Age-related Macular Degeneration (AMD) Audit: Feasibility Report

A report commissioned from The Royal College of Ophthalmologists National Ophthalmology Database Audit by the Healthcare Quality Improvement Partnership

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National Electronic Age-related Macular Degeneration (AMD) Audit: Feasibility Report

This feasibility study was commissioned by HQIP as part of a National Ophthalmology Audit with The Royal College of Ophthalmologists as the Audit Provider. Following feedback from NHSE minor amendments were made to this report in advance of its release in March 2018.

Executive Summary

The annual incidence in the UK of the "wet" or neovascular (NvAMD) form of AMD has been estimated as 39,700 new cases per year, a figure projected to rise by a third by 2020. NICE-approved treatments for "wet" NvAMD have included both ranibizumab (technology appraisal guidance 155) and aflibercept (technology appraisal guidance 294) on the basis of their clinical and cost effectiveness. In 2015−16, ranibizumab was second and aflibercept was fourth in the list of medicines with positive NICE technology appraisals on which the NHS spent most money, between them accounting for a total of around £450 million expended. Although some of these costs relate to use for other licensed indications, a sizable majority would have been for treatment of NvAMD and it is accepted that the cost impact of the use of these drugs for NvAMD is high https://www.nice.org.uk/guidance/ng82/resources/resource-impact-report-pdf-4724763661.

Prompt rescue and continued maintenance treatments for the condition are paramount to maintaining vision, delays to treatments frequently lead to irrecoverable visual loss and consequent higher costs of social support. In health care terms this requires:

1. Early diagnosis of NvAMD at a time prior to significant visual damage
2. Timely initiation and delivery of initial 'rescue' treatment with a 'loading dose' of 3 intravitreal injections within a relatively short space of time (weeks)
3. Ongoing timely regular disease monitoring and/or treatment to assess disease activity and adjust treatment intensity to maintain control of the condition.

Failure of services at any one of these stages can lead to permanent and irrecoverable loss of vision. Maintenance of vision is likely to require lifelong monitoring and treatment for successful long term control of the disease. The results reported here refer to both the processes of care outlined in 1-3 above and the visual outcomes of the eyes being treated. Apart from supportive care and optical enhancements there is currently no known effective treatment for "dry" AMD.

In this study to assess the feasibility of a national audit for treatment of NvAMD, data from 40 EMR enabled NHS centres were extracted. In eight centres insufficient numbers of patients were available for meaningful analysis, leaving 32 centres reporting on 9,243 patients undergoing first injections of either ranibizumab (Lucentis) or aflibercept (Eylea) during the two-year period from 01 January 2012 until 31 December 2013. The median (IQR) age was 82 (76, 87) years and baseline LogMAR acuity was 0.6 (0.8, 0.4) or ETDRS 55 (45, 65) letters or Snellen 6/24 (6/15, 6/38), with 64% being women. Data completeness varied among the centres with two thirds of centres (21) having follow-up data on 85% or more of treated patients at one year. Data completeness dropped off notably between one and two years after initiation of treatment. Specific reasons for loss to follow-up were unavailable, with older patients and those with worse vision at outset more likely to be lost to follow-up.

Outcomes

Primary and secondary audit outcomes were agreed through a stakeholder consultation exercise involving relevant professionals and patient representatives. Three primary and three secondary outcomes were identified:

Primary Outcomes

- Primary 'Good' outcome (preservation of vision i.e. effectiveness)
    - VA change from baseline (presentation) to one year, adjusted for age and starting VA
- Primary 'Bad' outcome (failure to preserve vision i.e. poor effectiveness)
    - VA loss of 0.3 LogMAR or worse (15 ETDRS letters or three Snellen lines)
- Primary 'Process' outcome (timely treatment)
    - Proportion of patients receiving three injections within three months of presentation

Secondary Outcomes

- Secondary 'Good' outcome (preservation of vision i.e. effectiveness)
    - Unadjusted VA change from month three to month 12
- Secondary 'Good' outcome (preservation of vision i.e. effectiveness)
    - Maintenance of VA at or above LogMAR 0.3 (70 ETDRS letters or Snellen 6/12)
- Secondary 'Bad' outcome (intra-ocular infection from injection i.e. safety)
    - Endophthalmitis rate

From electronically extracted data it was possible to produce results for the 32 centres for all primary and two of the three secondary outcomes. Caution should however be applied to these preliminary results, the main issue being higher losses to follow-up for around a third of centres, the importance of this being recognised in the fact that losses to follow-up were non-random creating potential for biased outcome reporting.

Feasibility of a National Audit of NvAMD Treatment

This study has illustrated that it would be feasible to undertake a National Audit of NvAMD treatment. Prompt diagnosis and initiation of treatment, followed by ongoing maintenance treatments are critical to achieving either visual acuity gains or preservation of vision. A prerequisite would be the provision of data collection tools for currently paper based centres in a similar way to the method employed for collection of National Audit Cataract Surgery data where audit tools were provided in the form of a speciailist EMR module and data collection template conforming to the nationally agreed minimum cataract dataset. The time frame for a NvAMD audit would be longer than for cataract surgery. From initiation of audit data collection there would be a necessary period to accumulate sufficient patients in each centre to make comparative analysis meaningful, following which the most recently included patients would need at least a 12 month follow-up period to determine outcomes and patterns of care. In addition to the primary and secondary outcomes noted above, data completeness would need to be reported as an additional metric with specified minimum requirements for centre eligibility. S251 exemption would be advisable to allow follow-up losses due to death to be positively identified.

In summary, this study has demonstrated the feasibility of a national audit for NvAMD. Certain prerequisites for data collection would be required and in addition to the identified primary and secondary outcomes a metric and benchmark for data completeness (timely follow-up) would be required.

National Electronic Age-related Macular Degeneration (AMD) Audit Feasibility Report

1. Background

Age-related macular degeneration (AMD) is the most common cause of certifiable visual impairment in the developed world. Until recently NvAMD was essentially untreatable with affected people losing central vision either rapidly from the "wet" variety or more slowly from the "dry" variety. The Hospital Episode Statistics for England alone reported 75,000 AMD related visits in 2013−2014, and the annual incidence in the whole of the UK of the "wet" or neovascular (NvAMD) form of AMD has been estimated as 39,700 new cases per year, a figure projected to rise by a third by 2020. NICE-approved treatments for "wet" NvAMD have included both ranibizumab (technology appraisal guidance 155) and aflibercept (technology appraisal guidance 294) on the basis of their clinical and cost effectiveness. In 2015−16, ranibizumab was second and aflibercept was fourth in the list of medicines with positive NICE technology appraisals on which the NHS spent most money, between them accounting for a total of around £450 million expended. Although some of these drug costs relate to use for other licensed indications, a sizable majority would have been for treatment of NvAMD and it is accepted that the cost impact of the use of these drugs for NvAMD is high https://www.nice.org.uk/guidance/ng82/resources/resource-impact-report-pdf-4724763661. Apart from supportive care and optical enhancements there is currently no known effective treatment for "dry" AMD.

Treatment for neovascular AMD is not a single procedure but requires ongoing timely maintenance therapy of injections into the vitreous cavity of the eye. Patients can be receiving these injections for many years. NICE guidance for both of the commonly used agents for "wet" NvAMD recommends that treatment should not be given when there is permanent structural damage to the centre of the macula, when the visual acuity (VA) is better than Snellen 6/12 or worse than Snellen 6/96 and/or when examination suggests that the treatment is not working. *Timely access to treatment is paramount for avoidance of severe vision loss and although some initial improvement of visual function is common at the start of treatment, the primary objective of treatment is to maintain vision at a reasonable level as opposed to restoration of full vision*. To achieve effective treatment, patients require an initial, loading phase series of three injections, given at monthly intervals, followed by a maintenance phase with further injection either as required, according to the clinical response, or in a fixed dosing regimen. For patients requiring ongoing follow-up and/or treatment at regular intervals, recent studies by both the Royal National Institute for the Blind and The Royal College of Ophthalmologists identified that many centres may not have adequate capacity to meet the demand. This can cause delays in both follow-up and treatment and have a negative impact on visual

outcomes https://www.rcophth.ac.uk/2017/02/bosu-report-shows-patients-coming-to-harm-due-to-delays-in-treatment-and-follow-up-appointments/.

In 2014, HQIP commissioned a National Ophthalmology Audit which included three feasibility studies for electronic audits in AMD, glaucoma and retinal detachment surgery, in addition to the main focus of the National Audit which was for cataract surgery. The feasibility studies were commissioned in order to assess the feasibility of undertaking national audits in these three conditions based purely on data extracted from specialty specific electronic medical record systems (EMRs). This report is based on multicentre data collected as a by-product of routine clinical work using the Medisoft EMR.

2. Context of the Feasibility Studies

The National Ophthalmology Database Audit is primarily concerned with publishing comparative cataract surgical results for named surgeons (excluding trainees) and named centres (including trainees) and forms part of the Consultant Outcomes Publication (COP). The main cataract surgical audit and the three feasibility studies use routine clinical care data extracted from specialty specific EMR systems. By far the most widely used system is the Medisoft EMR, with the OpenEyes EMR currently contributing data from a single very large centre, with a small number of bespoke local databases also providing data. The remit of the feasibility studies is to investigate the feasibility of the use of data derived exclusively from EMRs to assess the potential for future full scale national audits in one or more of these three topics.

The audit provider is The Royal College of Ophthalmologists (RCOphth) and the College has engaged a number of subcontractors to deliver various elements of the audit. The brief from the audit commissioners included a requirement that these audits should build on the work of The RCOphth National Ophthalmology Database project which previously extracted, aggregated and analysed EMR derived data and published surgical benchmarks for a number of high volume ophthalmological procedures. A small working group based at The RCOphth obtains permissions and coordinates the work in conjunction with the 'NOD Delivery Unit' based in Cheltenham, the EMR providers Medisoft and OpenEyes, and a web design company. The NOD Delivery Unit forms the 'engine room' of the audit where the extracted data are aggregated and analysed following extraction by the EMR providers. The Medisoft EMR cataract module and optometric data return tools are provided as needed by the audit to allow currently paper based centres to collect data as part of routine clinical activity. The national audit is overseen by a RCOphth based multi-professional steering committee with Patient and Public Involvement (PPI) which reports via the Informatics and Audit

sub-committee to the Professional Standards Committee and ultimately to the College Council. Regular contract review meetings are held with the audit commissioners.

3. Aims of the NvAMD Feasibility Audit

- To assess the feasibility of auditing the outcomes of intravitreal injection treatment for wet NvAMD in multiple EMR enabled centres

4. Stakeholder Engagement

In February 2016, an AMD Audit stakeholders meeting was held at the RCOphth. The purpose of the meeting was to engage with the relevant stakeholders, and in the interests of avoiding re-invention of wheels, to harvest the methodological and other wisdom from various collaborative groups with experience and established track records of working with EMR derived NvAMD data. It was anticipated that candidate audit outcome metrics for NvAMD would emerge through group discussion. The invitation was circulated to 20 relevant experts and patient representatives (e.g. Macular Society), most of whom were able to join the meeting either face-to-face or by teleconference. A number of individuals who were unable to join provided written comments. Additional comments and suggested outcome measures were also obtained from lay member of The RCOphth and Vision 2020 UK group. From the meetings and subsequent email discussions several themes emerged.

4.1 Desired Principles for the Audit as expressed by the Stakeholder Group

- Eligibility criteria should be as wide as possible (inclusion and exclusion criteria to be defined)
- Comparisons should be at centre level (not individual consultants as ongoing care is provided by teams, including medical retina consultants, trainees and non-medically qualified staff)
- Outcomes should take precedence over process measures
- VA to be reported in LogMAR and EDTRS letters (Snellen can be converted to LogMAR)
- Access to services (initial VA) and effectiveness (preservation of VA) to be assessed
- All NvAMD treatments should be included if possible
- First and second eyes should be analysed separately
- Attrition of populations should be taken into account
- Minimum dataset to achieve audit aims should be defined in due course
- No additional data collection should be required (only use data already collected in EMRs)
- HES workload burden should be quantified (e.g. injections / year; visits / year)
- Safety should be included (e.g. endophthalmitis rate if data available and/or significant VA loss)

- PROM collection (e.g. ICHOM Standard Set for Macular Degeneration) is currently not feasible but to be considered for the future.

A long list of candidate outcome metrics was harvested from group discussion and appears in Appendix 1.

5. Methodology

5.1 Data extraction from EMRs

The data for these analyses was initially extracted from the Medisoft EMR in autumn 2015 with a supplementary extraction in February 2016 to resolve a number of issues in the original extraction.

NvAMD data were extracted from 40 NHS centres covering the period from initial installation of the EMR (which varied by centre) up to 31 March 2015. The data files for analysis included:

- Patient details
- Indications for surgery
- Ocular co-pathology
- Operative procedures
- Injections
- Visual acuity
- Operative complications
- Post-operative complications

6. Results

6.1 Inclusion and exclusion criteria for the analysis

In order to allow for at least one full year of follow-up for patients with a first injection of either ranibizumab (Lucentis) or aflibercept (Eylea), and to enable the analyses to reflect recent patient experience the analysis was restricted to individuals with a first injection of either drug in their first or second eye to be treated during the two year period from 01 January 2012 until 31 December 2013. For patients who received their first treatment in both eyes simultaneously on the same date, the better of the two eyes was included. Patients were not included in these analyses if they were ever treated with bevacizumab (Avastin, not

licenced for use in NvAMD) or dexamethasone (Ozurdex, a steroid with different mode of action and unlicensed for use in NvAMD).

6.2 Data Cleaning

A number of data issues became apparent and for these reasons the analysis set was restricted to those with data which appeared to be likely to be reliable. The injection set of data included "number of previous injections". For a treatment naive patient these should then be 0, 1, 2, 3, 4 etc. For some patients the first injection in the data was a number greater than 0 but then incremented as one would expect, so 7, 8, 9, 10. These patients most likely started their treatment before the introduction of the EMR in that centre and these were excluded from the data analyses. There were other patients where the numbers were not consecutive and this may have been where records were kept elsewhere for some of the time or patients had been treated in another centre. These patients were also excluded. Centres with fewer than 100 treatment naive patients satisfying the inclusion criteria were excluded. From the original 40 centres, 32 were considered to be eligible for inclusion. Centre numbers were assigned in order of cohort size, thus centre one has most patients. These centres comprise the analysis sample.

6.3 Characteristics of the initial analysis sample

There were 9,243 patients in the 32 centres undergoing injections in affected eyes who had VA measurements recorded. The median (IQR) age was 82 (76, 87) years and baseline LogMAR acuity was 0.6 (0.8, 0.4) or ETDRS 55 (45, 65) letters or Snellen 6/24 (6/15, 6/38), with 64% being women (Figures 1 and 2, Appendix 2 for VA conversions). Published data indicate that a number of baseline factors influence visual acuity outcomes, including baseline VA and age, as well as the subsequent treatment regime. Median age at baseline varied between centres from 80 to 84 years and median baseline LogMAR acuity from 0.48 to 0.70 (61 to 50 ETDRS letters). The Index of Multiple Deprivation (IMD) varied by centre, Figure 3 with increased deprivation being clinically insignificantly (R^2=0.04) associated with worse VA at presentation (this small effect was statistically significant but deemed unimportant).

Figure 1. The distribution of age by centre

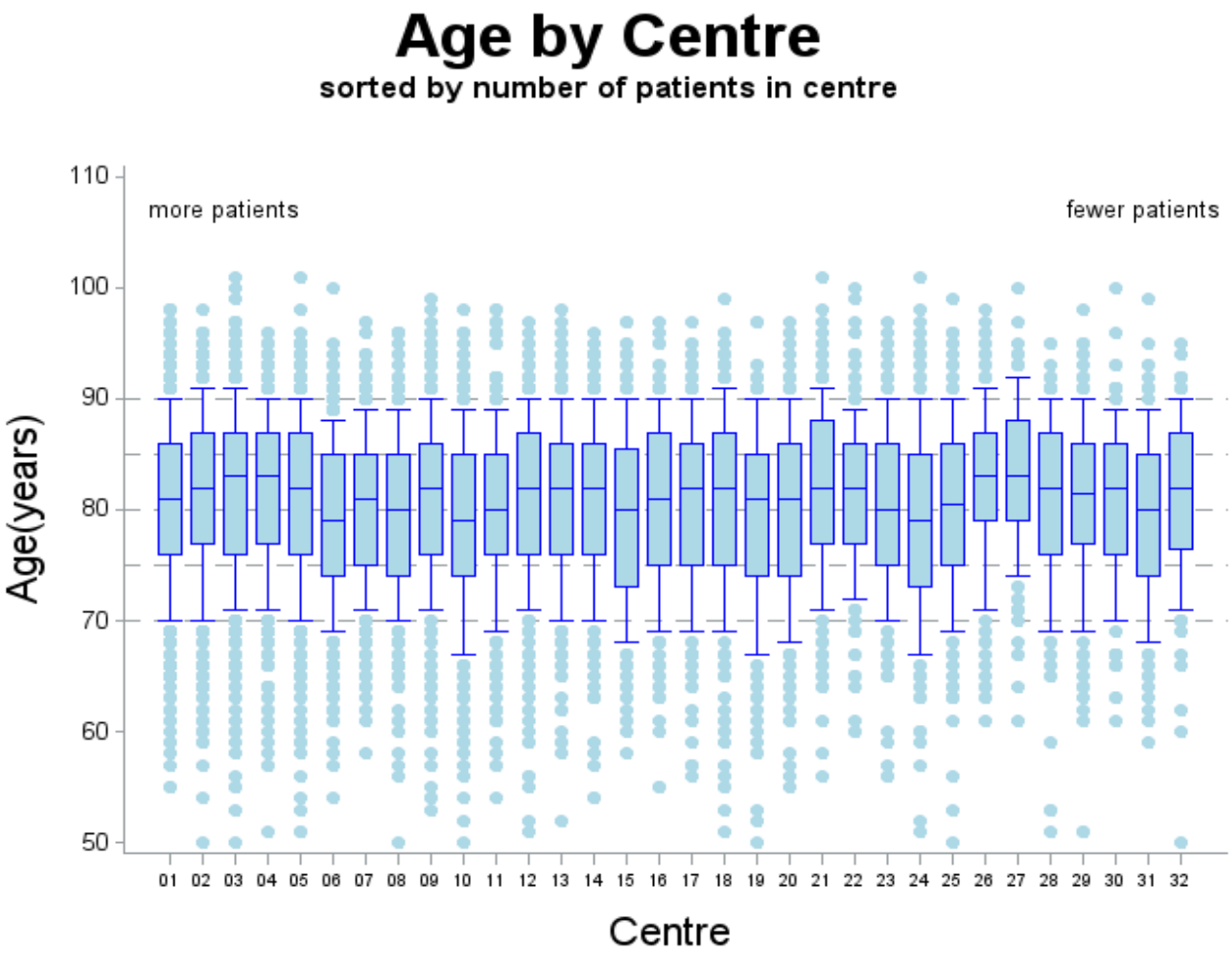


Figure 2. The distribution of baseline LogMAR VA by centre (latest VA prior to first injection, provided within 14 days of injection)

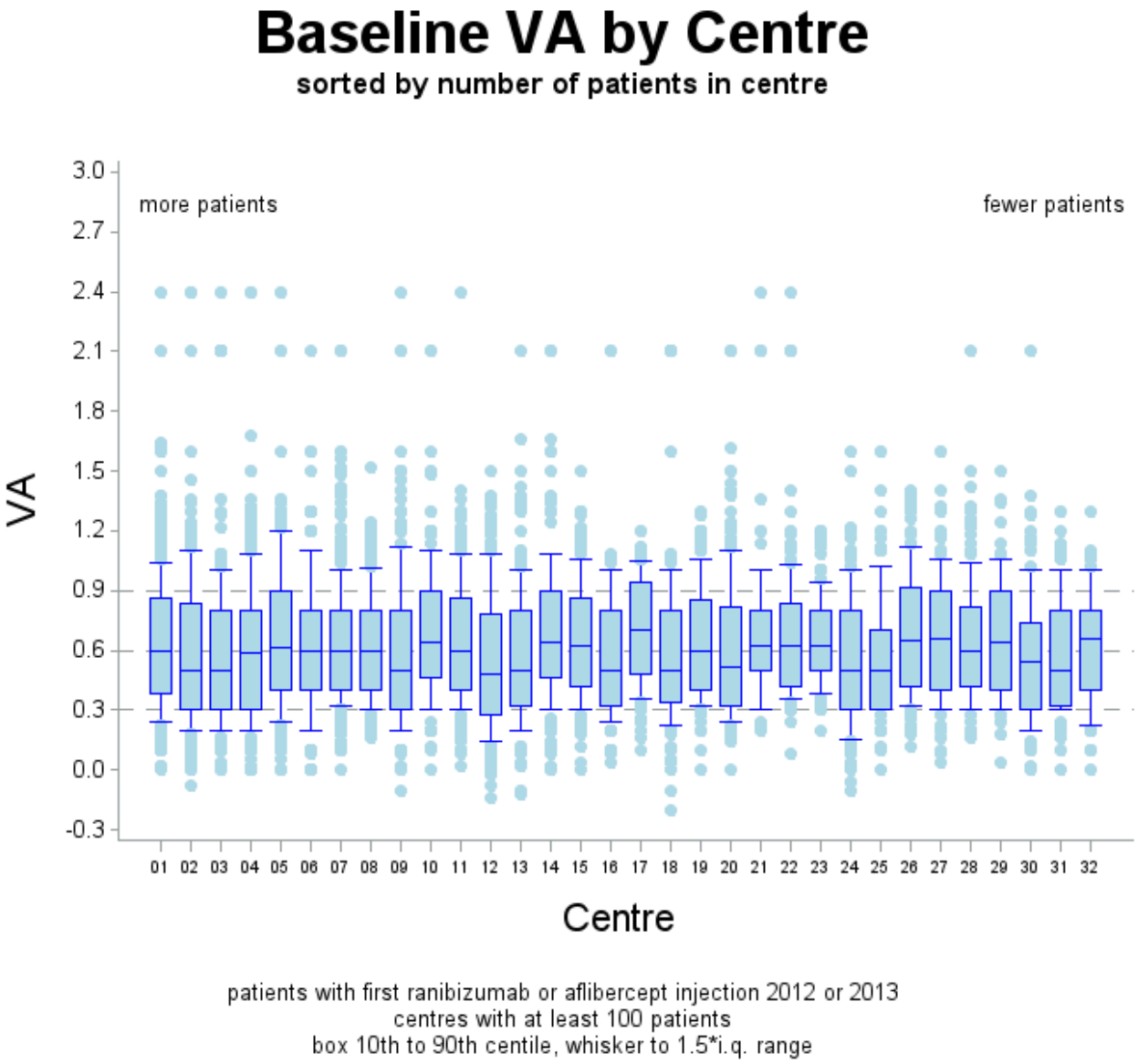
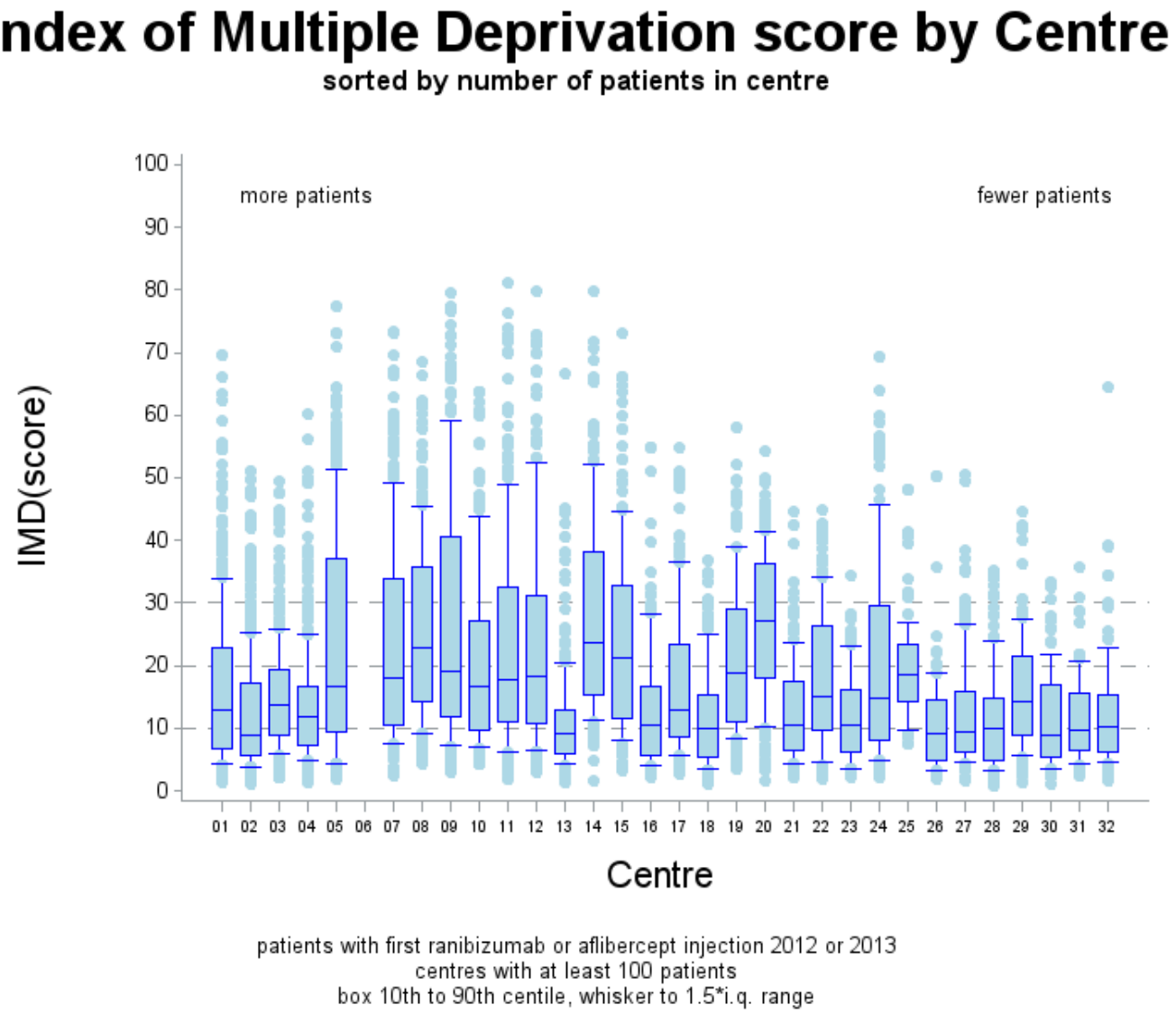


Figure 3. Index of multiple deprivation (IMD) score for centres

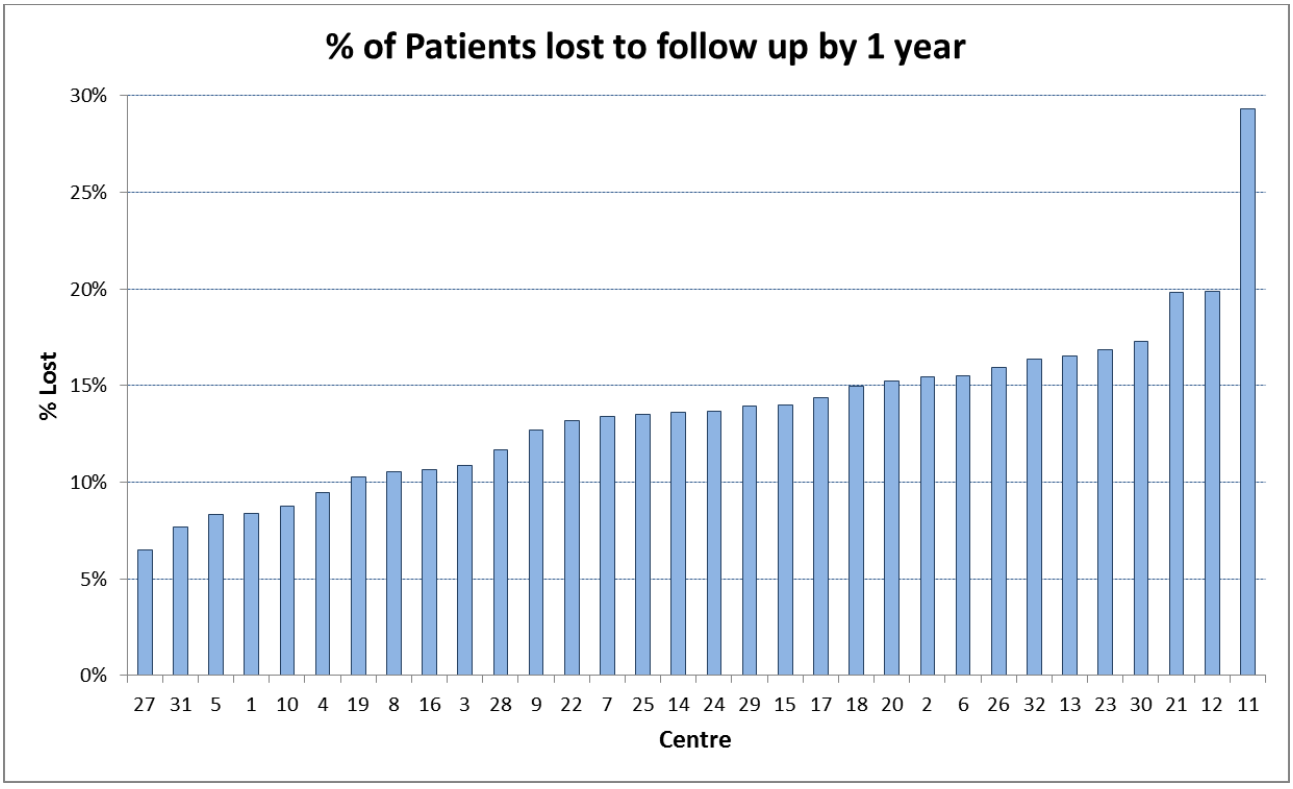


6.4 Data Completeness – Losses to follow-up

Patients were considered as 'lost to follow-up' if the EMR record of their care ended abruptly with no further clinical data recorded after a certain point in time. Although it is possible that these patients had been seen but without any data entry into the EMR, these visits were assumed not to have taken place for the purpose of analysis. (The Medisoft EMR does allow clinicians to identify when an active decision has been taken to stop treatment but this information was not available as part of this data extraction.)

Loss to follow-up with incomplete data creates difficulties in terms of the data analysis. Initial analysis indicated that patient loss to follow-up appeared to be a significant problem in several centres. High rates of loss to follow-up undermine certain potential outcome metrics which [makes] this an important issue to understand. This problem accelerates rapidly during the second year of follow-up in all centres and analyses have therefore been confined to the first year of treatment for which 87% of patients overall had follow-up data. In a few centres notable losses occurred even during the first year, Figure 4. For centre 11 for example, the majority of the last 150 or so patients were seen for less than a year and some not seen at all after their third injection.

Figure 4. Losses to follow-up at one year by centre



Data are not available to explain why patients were lost to follow-up. Only six of 32 centres have any patients reported as having died, within which proportions having died ranged from 0.5% to 7%. Based on residual life expectancy for similarly elderly people around 5% of patients may be expected to be lost within a year due to death[1]. At most of the centres reported here, losses within the first year substantially exceeded this rate. It is likely that there would be diverse reasons for this such as systemic co-morbidities and difficulties with transport as well as treatment failure with patients or their doctors 'giving up' on the treatment and patients either discharging themselves or being discharged by the care team.

Biases were observed in regard to the missing data. Using VA of LogMAR 0.3 (70 ETDRS letters or Snellen 6/12) or better at 12 weeks after their first injection as the reference group, those with vision worse than this level at 12 weeks were more likely to be lost to follow-up. Using those under 75 as the reference group, older people were more likely to be lost to follow-up, Table 1. There was no association between IMD and loss to follow-up. With so many patients failing to attend for a year past their third injection, and the pattern of missing information being non-random, caution should be exercised when interpreting unadjusted mean changes in VA as these may be misleading as a measure of the effectiveness of a centre.

Table 1. Risk factors for loss to follow-up

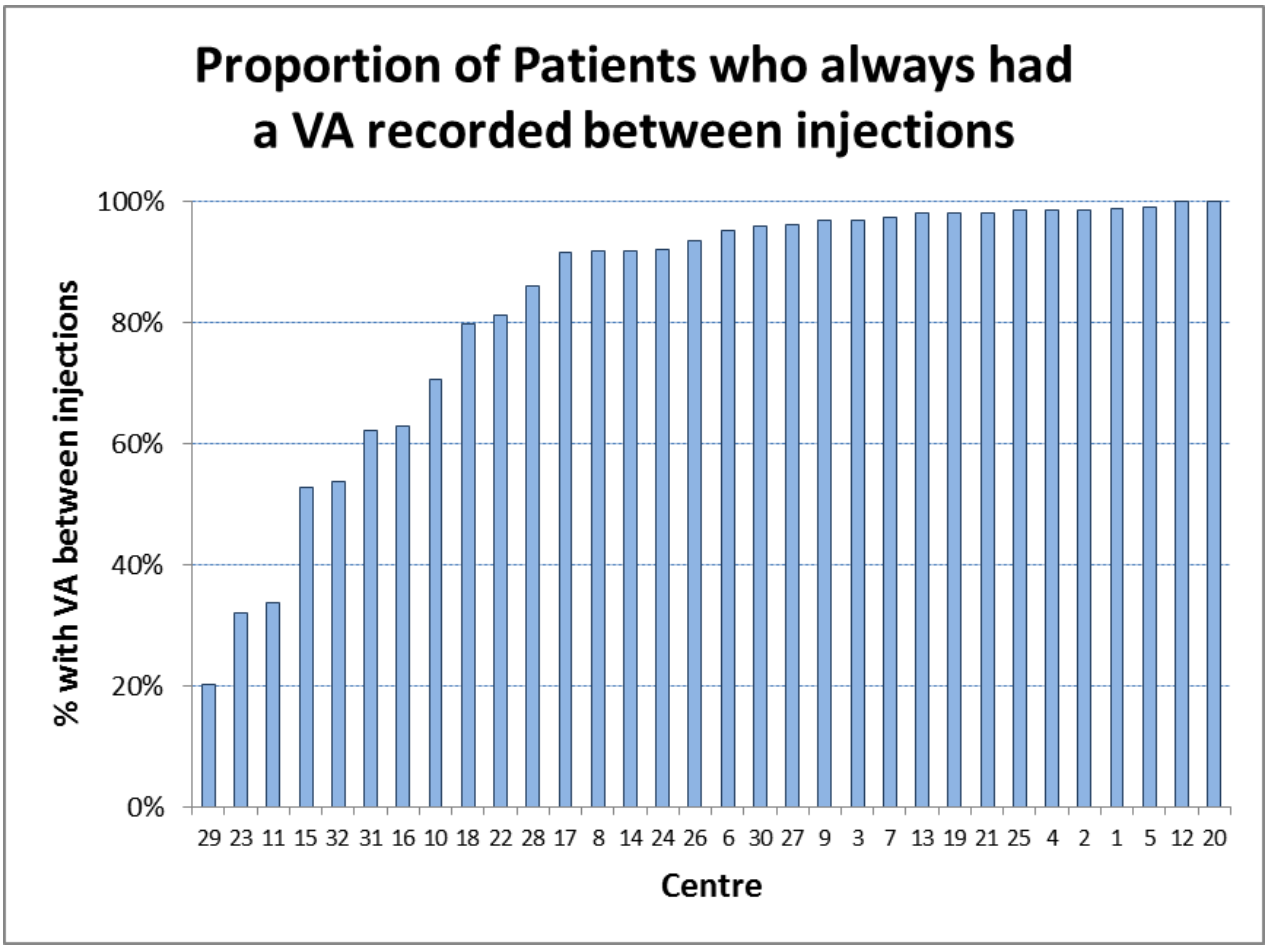
Cox proportional hazards model – time to last record of attendance		
Group	Hazard ratio	P value
VA better than 0.3 at 12 Weeks	1.00	(reference group)
VA 0.3 to 0.59	1.16	0.03
VA 0.6 to 0.89	1.51	<0.0001
VA 0.9 or worse	2.72	<0.0001
Age under 75	1 (reference group)	(reference group)
75 to 79	0.96	0.63
80 to 84	1.29	0.0004
85 to 89	1.80	<0.0001
90 and above	2.53	<0.0001

[1] Office of National Statistics: For people aged 80 years the probability of death in the next year for a man is 6% and for a woman is 4%. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables

6.5 Data Completeness – VA recorded between injections

Normal practice would dictate that VA would be recorded to inform the decision whether to proceed with the next injection or otherwise. It would therefore be expected that there would be at least one record of a VA measurement between one injection and the next. This was not always the case with some centres not recording VA data on the EMR between injections. Variations in patient pathways could explain this. For example, VA might be assessed and recorded on paper notes but not entered into the EMR. Whatever the explanation for this phenomenon, the outcome in terms of missing VA data is apparent in the EMR extracted data as seen in Figure 5 where missing VA data between injections varied between centres from an extreme of 80% missing (one centre) to never missing a VA between injections (two centres). Overall, 87% of patients always had a VA measurement either on the day of an injection or since the previous injection.

Figure 5. Proportion of patients who always had VA recorded prior to an injection for centres



6.6 Data Completeness – Approach to missing data

The levels of missing data beyond one year were deemed unacceptable and for this reason the analysis was confined to the first year of data following the initial injection. Within the first year the pattern of loss to follow-up was not random with older patients and those with worse initial vision being more likely to be lost to follow-up. Multiple imputation methods were considered, but not employed, because doing so would render the results difficult for clinicians and the public, who may be unfamiliar with statistical methodology, to understand and interpret. As a pragmatic solution, the results for centres with different levels of missing data have been grouped in order to aid interpretation of the results as presented.

6.7 Outcomes

Primary and secondary candidate outcome metrics were chosen based on stakeholder input, discussion with experts and available data.

Published clinical trial and cohort reports suggest that visual acuity typically increases during the initial loading phase of treatment. During the subsequent, maintenance phase of treatment, visual acuity either remains stable or decreases slowly as a consequence of disease progression or co-existing ocular pathology. Early visual acuity gains are typically greater in eyes with worse baseline acuity and smaller in the eyes with better baseline acuity. Given the variation in baseline median VA between centres, a simple comparison of VA change from baseline was felt to be a potentially biased method of comparing outcomes between centres. VA data for each centre are illustrated graphically in 'bubble plots' at baseline versus at one year in Appendix 3.

6.71 Primary Outcomes

- Primary 'Good' outcome
    - VA change from baseline (presentation) to one year, adjusted for age and starting VA (preservation of vision i.e. effectiveness)
- Primary 'Bad' outcome
    - VA loss of 0.3 LogMAR or worse (15 ETDRS letters or three Snellen lines; failure to preserve vision i.e. poor effectiveness)
- Primary 'Process' outcome
    - Proportion of patients receiving three injections within three months of presentation (timely treatment).

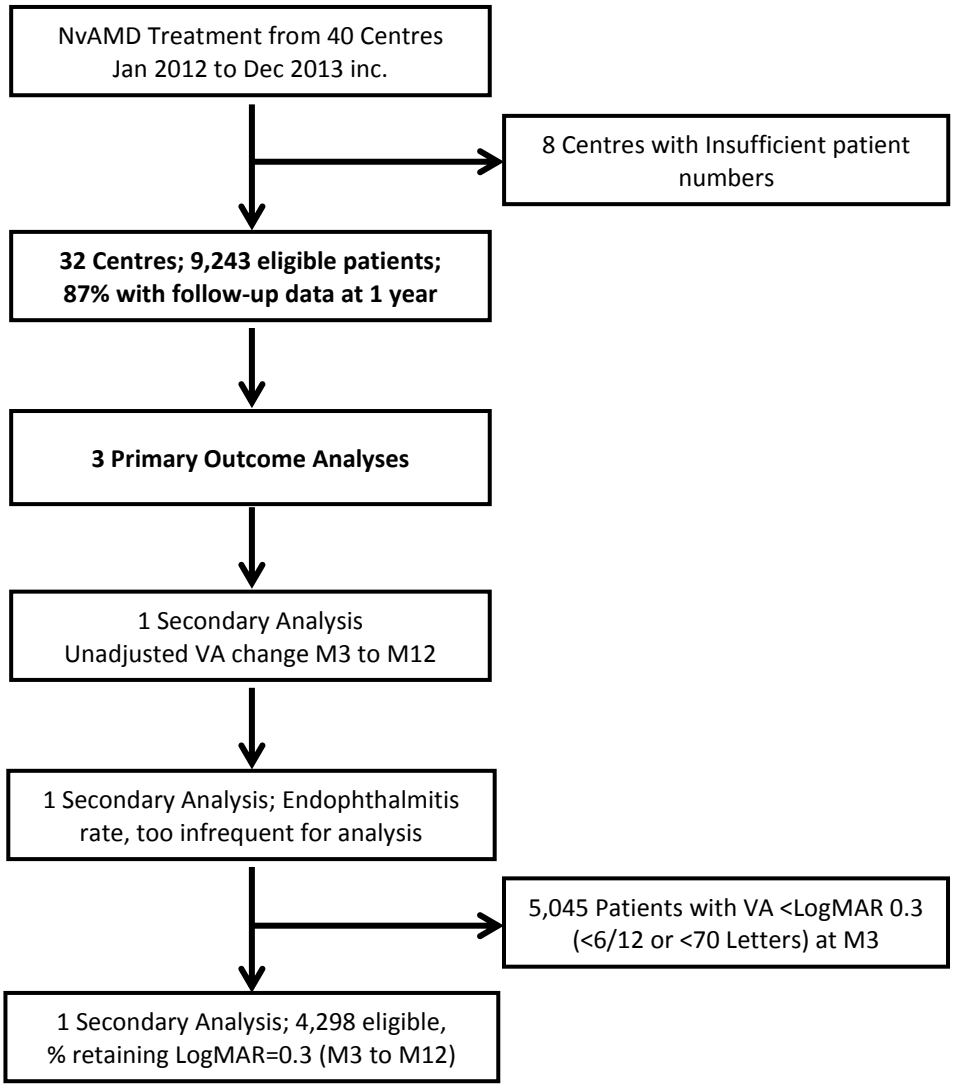
6.72 Secondary Outcomes

- Secondary 'Good' outcome
    - Unadjusted VA change from month three to month 12 (preservation of vision i.e. effectiveness)
- Secondary 'Good' outcome
    - Maintenance of VA at or above LogMAR 0.3 (70 ETDRS letters or Snellen 6/12; preservation of vision i.e. effectiveness)
- Secondary 'Bad' outcome
    - Endophthalmitis rate (intra-ocular infection from injection, safety)

6.73 Eligibility for Outcome Groups

The groups of patients eligible for the various stages of the analysis are summarised in Figure 6 in the form of a flow chart.

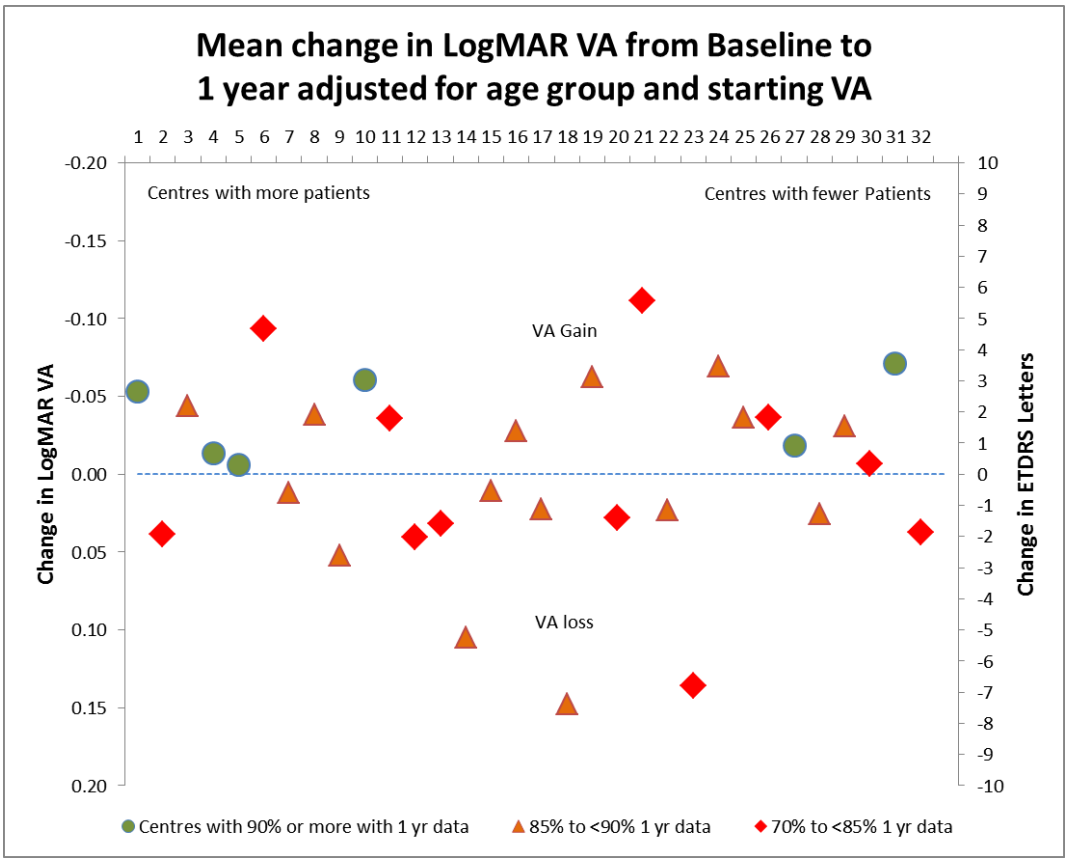
Figure 6. Flow chart showing eligibility for various elements of the analysis of outcomes



6.8 Primary 'Good' Outcome Metric

Since the purpose of treatment is vision preservation, the desired primary effectiveness outcome was visual acuity change from baseline to month 12, adjusted for starting acuity and age. In view of concerns regarding incomplete follow-up and the observed biases affecting follow-up, the outcome metrics were analysed and are presented in strata based on the completeness of the data for each centre as seen in Figure 7. Of the 32 centres analysed, six centres had follow-up data completeness of 90% or more, 15 centres had completeness of 85% to <90% and 11 centres had completeness of 70% to <85%. People who have worse visual outcomes and those who are older are less likely to continue to attend. In centres with a high proportion of patients who have been lost to follow-up, those who remain would overall have better vision and would be younger. Thus, if people lost to follow were excluded from the analysis an inaccurate and biased (too favourable) report would result for those centres with significant numbers of follow up losses.

Figure 7. Mean change in VA between baseline (month 0, i.e. prior to first injection) and month 12 adjusted for age group and baseline VA and stratified by completeness of follow-up data for centres.



In this analysis, a 'Good' outcome can be regarded as preservation of VA within LogMAR 0.1 (5 letters or one line on the chart) of baseline. Data completeness of 90% or more provides a high level of confidence in the reported results. In the plot adjusted for age and starting VA, it is of note that the six centres with this level

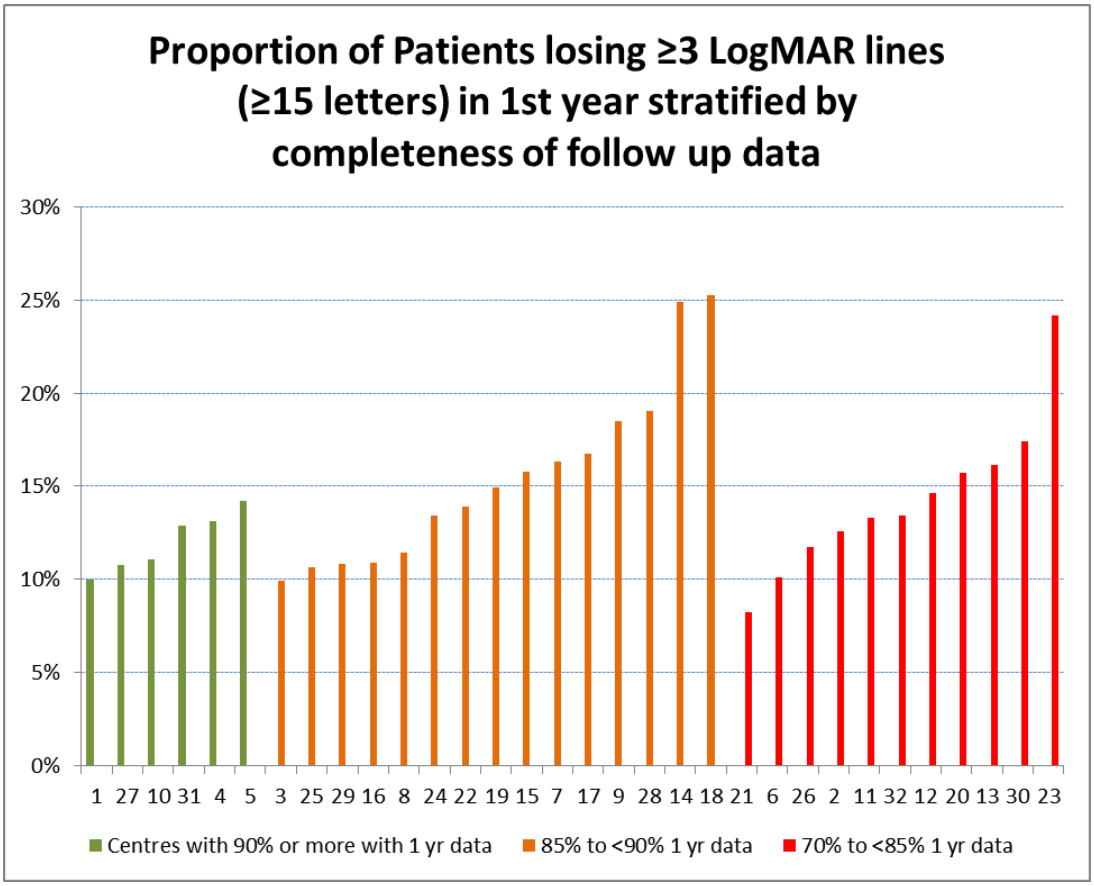
of data completeness are all well performing centres. In these six centres, there were modest gains in mean visual acuity at one year, from less than one to more than three ETDRS letters at month 12. Centres with less data completeness display wider variation in performance overall in terms of visual acuity change from baseline to month 12, with three centres on average falling below the five letter threshold for 'Good' outcome. No centre fell below 10 letters loss on average which appears encouraging although the question of missing data should be borne in mind when interpreting these results.

6.9 Primary 'Bad' Outcome Metric

Since the purpose of treatment is preservation of vision, a metric of poor outcome would be loss of vision. A loss of 0.3 LogMAR units or more (15 ETDRS letters or three Snellen lines) is regarded as a standard for moderate loss of vision. A loss of ≥0.3 LogMAR has thus been chosen as a primary metric for a 'bad' outcome indicating failure to preserve vision. Since older people and those with worse starting VA are more likely to be lost to follow-up, centres in Figure 8 have been grouped according to the percentage of patients lost to follow-up at one year. Selective losses to follow-up of older people and those with worse outcomes may bias this metric by artefactually inflating performance. For the six centres with more than 90% data completeness at one year, the percentage of patients experiencing moderate visual loss or worse at one year in the first treated eye varied from 10-14%. Much wider variation was observed in the centres with less complete data entry.

Using these data, a Cox regression model for time to loss of three lines indicates that older age and worse VA at baseline are independently associated with a worse outcome, with number of injections, as expected, providing a powerful protective effect. For example, people over 90 years have around a 30% increased risk of vision loss compared with those aged under 85 years and those with VA worse than 0.60 at baseline have around a 25% increased risk of vision loss compared with those whose starting VA is better than 0.60 LogMAR. Each injection reduces the risk of vision loss by around 9%, a result that stresses the importance of monitoring and timely treatment.

Figure 8. Percentage of eyes losing ≥ 3 LogMAR lines (≥ 15 letters = experiencing moderate visual loss) between baseline and month 12. As many as 25% of patients in certain centres experience moderate loss of vision in contrast to other centres where this occurs in only around 10% of patients.



6.10 Primary Process Metric

Both professional and lay representatives were keen that delays in follow-up be included as a process measure. The difference between the planned follow-up and the actual follow-up interval is available as an audit within the Medisoft EMR but this information was not captured as part of this data extraction. The recommended time for the initial loading dose of three injections is in the first eight weeks. Completion of the first three injections can thus be used as a process metric for completion of the loading phase of treatment. Allowing for some 'real world' slippage past the eight weeks, Figure 9 indicates the proportion of patients who achieve three injections within 12 weeks for each centre. For the six centres with the most complete data entry, between 93 and 98% of eyes were given all three injections within this 12 week period. Apart from centres two and 20, all the other centres achieved a figure over 80% of patients having three injections within this 12 week period. Table 2 provides the actual times for each centre for 25%, 50% and

75% of patients to achieve three injections. Centres two and 20 appear to underperform significantly on this process measure for initiation of treatment.

Delivery of injections is a critical element in the treatment pathway. Overall the median number of injections in the first year from commencement of treatment was six (IQR 4, 7), the number for each centre is provided in Table 3.

Figure 9. Proportion of patients receiving initial three injections in 12 weeks

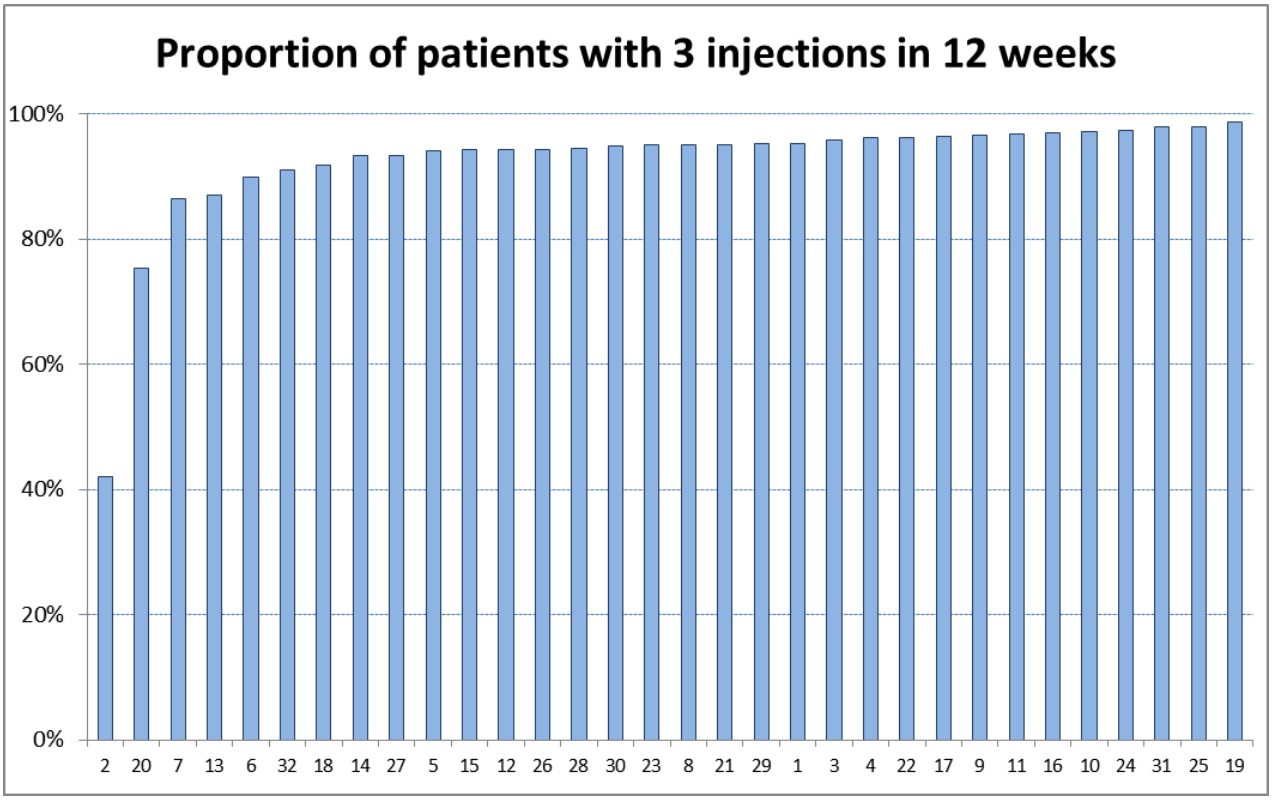


Table 2. Time for 25%, 50%, 75% of patients in each centre to reach their third injection. (Recommended timing for the first three injections is completion within eight weeks.)

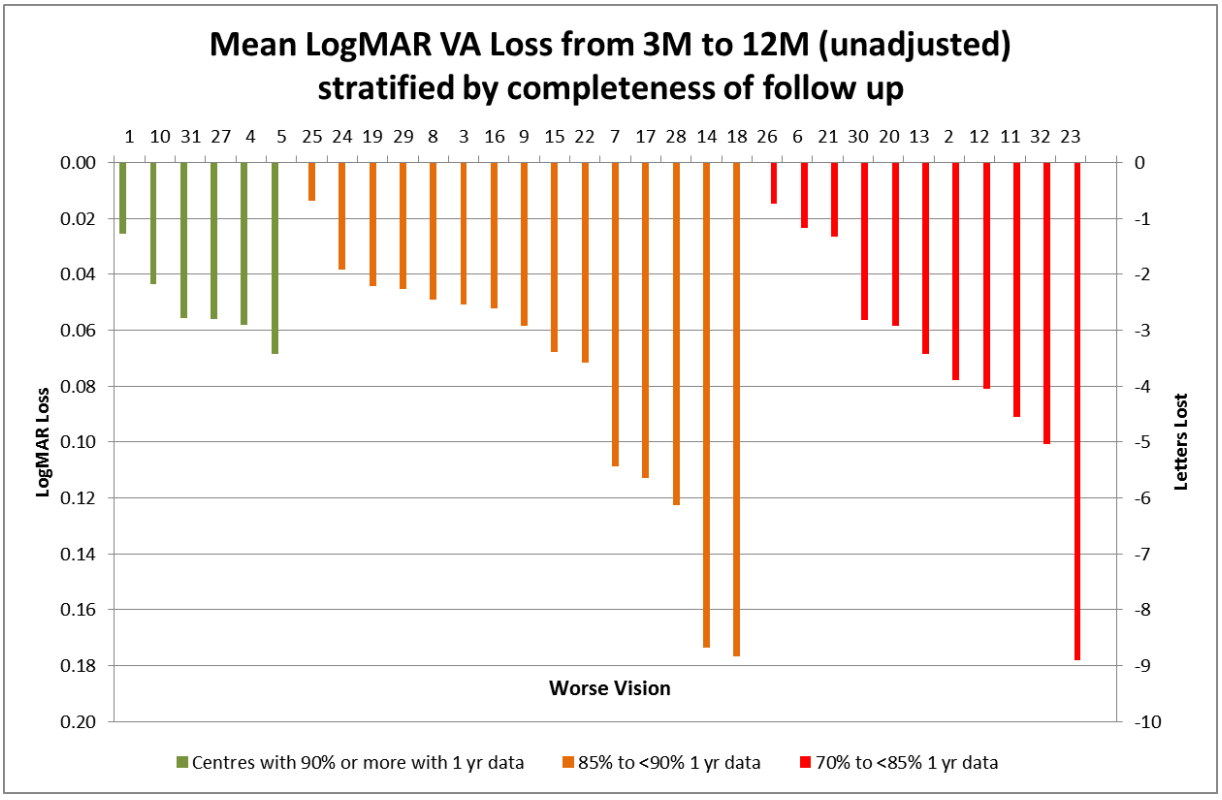
Centre	Time to 25% having third injection (weeks)	Time to 50% having third injection (weeks)	Time to 75% having third injection (weeks)
1	8	9	9
2	9	20	71
3	8	8	9
4	8	8	9
5	8	8	9
6	9	10	11
7	8	9	11
8	8	9	9
9	9	9	10
10	8	9	9
11	8	9	10
12	8	8	9
13	8	9	10
14	9	10	11
15	8	9	9
16	8	8	9
17	8	9	10
18	9	9	10
19	8	9	9
20	8	9	17
21	8	8	9
22	8	8	9
23	8	9	9.5
24	8	9	9
25	8	9	9
26	8	9	10
27	8	9	10
28	8	8	9
29	9	10	10
30	8	9	10
31	8	9	9
32	8	9	9

In centre two at one year from the first injection 31% of patients have not reached their third injection. In centre 20 at one year 13.6% have not had a third injection.

6.11 Secondary outcomes

Two candidates for secondary 'Good' outcomes were proposed and one for a 'Bad' secondary outcome. The first secondary 'Good' outcome was visual acuity change from month three to month 12, unadjusted for starting acuity and age, Figure 10. In view of concerns regarding incomplete follow-up and the observed biases affecting follow-up, the outcome metrics were analysed in strata based on the completeness of the data for each centre. As expected, for all centres there is some deterioration of VA following the initial gains associated with the loading phase of treatment. In the six centres with most complete data entry, the mean unadjusted change in acuity from months three to 12 varied from one to just over four ETDRS letters. Selective losses to follow-up of older people and those with worse outcomes may bias this metric by artefactually inflating performance in centres with high levels of loss to follow-up.

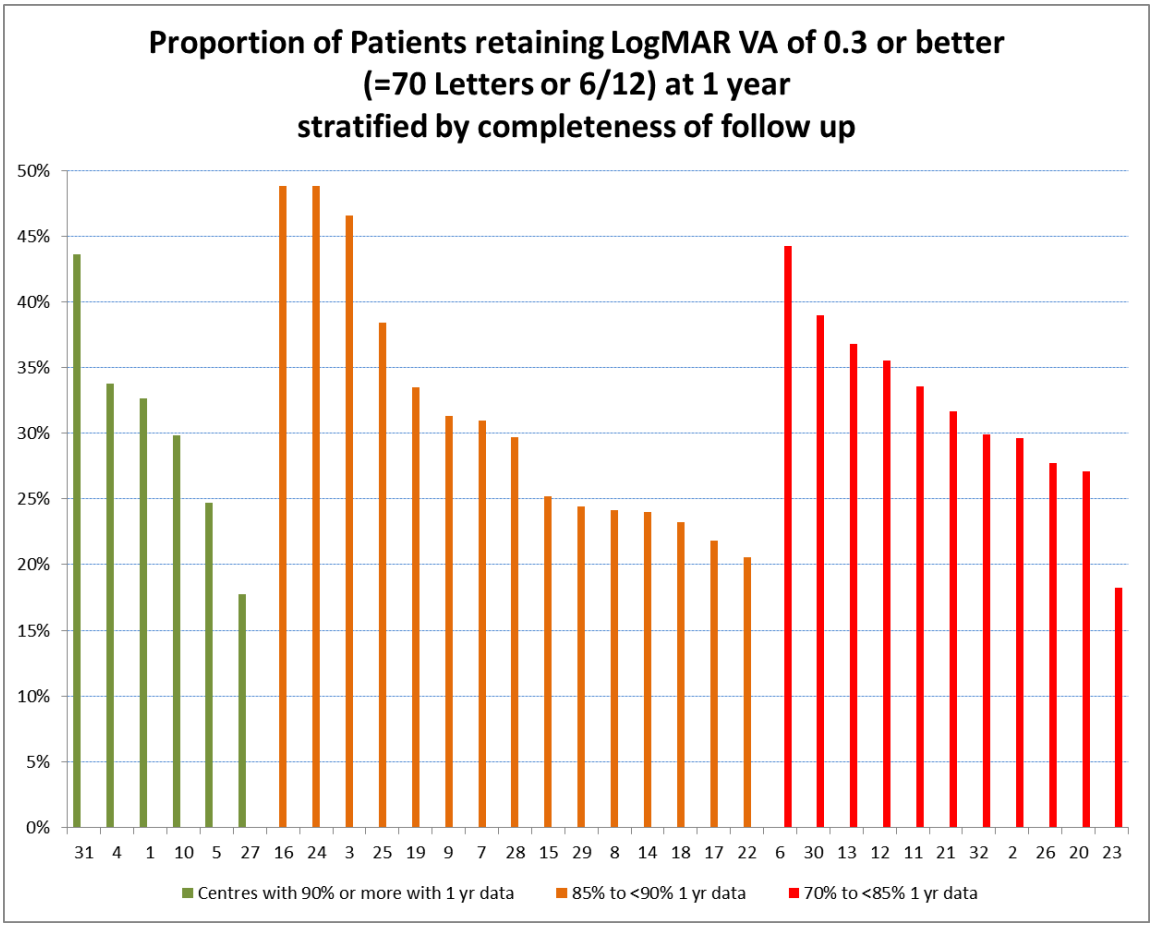
Figure 10. Visual acuity change from month three to month 12, unadjusted for starting acuity and age



The other secondary 'Good' outcome was retention of a visual acuity of LogMAR ≥0.3 (70 ETDRS letters or Snellen 6/12) at one year which approximates to the current DVLA requirement for driving vision. In Figure 11 this outcome is presented in strata based on the completeness of the data for each centre. Eligibility for this analysis was LogMAR ≥0.3 at three months (i.e. following loading dose treatment). Overall, only 46% of patients met the entry criteria for this analysis and of these just 33% retained LogMAR ≥0.3 at 12 months.

For the six centres with more complete data entry, the percentage of eyes with this level of visual acuity at the end of the first year of treatment ranged from 18% to 44%. Greater variation was observed in the other strata. Some of this variation may be explained by the percentage of eyes with this level of visual acuity at the start of treatment and selective losses to follow-up of older people and those with worse outcomes may bias this metric by artefactually inflating performance. Overall, for the 4,298 patients with acuity of LogMAR 0.3 (70 ETDRS letters) or better after the loading phase of treatment, it took 14.1 months for 15% to drop below this level. Times for individual centres are listed in Table 3.

Figure 11. Secondary 'Good' outcome of the percentage of patients retaining VA of 70 letters by centre ordered by completeness of follow-up data and centre performance against this metric



The secondary 'bad' outcome proposed was the endophthalmitis rate. There are concerns that case ascertainment for this may be a problem. In the NHS year 2012/13, based on 20,534 injections in the cohort there were 27 identified cases =1.3 per 1,000 injections. Previous publications have reported incidence figures of below 0.1% (less than one in 1000). There are not enough cases to examine the rates in individual centres therefore as a comparative metric this is of limited value.

The key metrics from the audit are summarised in Table 3 for each centre.

Table 3. Summary data for centres

	Data Quality			Process		Injections in 1 year			VA Change ETDRS Letters (1 Letter = 0.02 LogMAR)		Loss of LogMAR VA ≥0.3 or ≥15 letters		Retention of LogMAR VA ≥0.3 or ≥70 letters		
Centre	% lost FU 1 Year	N with data at 1 year	% always VA prior injection	% 3 injections by 12 weeks	Time to 75% having third injection (weeks)	Median number injections	25th centile	75th centile	Mean change in VA 0M to 12M adjusted for starting VA and age (-ve = worse)	Mean unadjusted drop in VA 3M to 12M	% Lost ≥0.3 or ≥15 letters in 1 Year	Time in months for 5% to lose ≥0.3 (≥15 letter) from first injection	% with VA ≥0.3 (≥70 letters at) 3 months	% retaining VA ≥0.3 (≥70 letters) at 1 Year	Time in months for 15% to drop below VA of LogMAR 0.3 (70 letters)
1	8.4%	625	99%	95%	9	6	5	8	2.7	-1.3	10%	6.4	36%	33%	15.1
2	15.5%	421	99%	42%	71	5	2	8	-2.0	-3.9	13%	4.7	87%	30%	13.5
3	10.9%	521	97%	96%	9	6	4	7	2.2	-2.6	10%	5.4	52%	47%	14.5
4	9.4%	524	99%	96%	9	6	4	8	0.7	-2.9	13%	6.0	45%	34%	14.9
5	8.3%	480	99%	94%	9	6	4	8	0.3	-3.5	14%	5.3	32%	25%	14.4
6	15.5%	365	95%	90%	11	6	4	7	4.7	-1.2	10%	4.7	54%	44%	13.6
7	13.4%	332	97%	87%	11	6	4	7	-0.6	-5.5	16%	4.3	67%	31%	13
8	10.5%	348	92%	95%	9	6	4	7	2.0	-2.5	11%	4.9	54%	24%	14
9	12.7%	321	97%	97%	10	6	3	7	-2.6	-3.0	19%	4.6	82%	31%	13.4
10	8.7%	332	71%	97%	9	5	4	7	3.1	-2.2	11%	5.9	38%	30%	14.9
11	29.3%	243	34%	97%	10	5	4	7	1.8	-4.6	13%	2.6	79%	34%	8.8
12	19.9%	243	100%	94%	9	4	3	6	-2.0	-4.1	15%	4.2	70%	36%	12.6
13	16.5%	215	98%	87%	10	6	3	8	-1.6	-3.5	16%	3.4	63%	37%	11.2
14	13.6%	224	92%	93%	11	5	3	7	-5.3	-8.7	25%	4.6	43%	24%	13.5
15	14.0%	218	53%	94%	9	6	4	7	-0.6	-3.4	16%	5.4	36%	25%	14.5
16	10.6%	211	63%	97%	9	7	5	9	1.4	-2.6	11%	5.5	61%	49%	14.5
17	14.3%	191	92%	96%	10	4	3	5	-1.1	-5.7	17%	5.5	66%	22%	14.6
18	15.0%	197	80%	92%	10	5	4	7	-7.4	-8.9	25%	4.3	45%	23%	12.9
19	10.3%	205	98%	99%	9	6	4	7	3.1	-2.2	15%	3.5	38%	33%	11.4
20	15.2%	179	100%	75%	17	5	4	7	-1.4	-2.9	16%	4.7	43%	27%	13.6
21	19.8%	161	98%	95%	9	6	4	7	5.6	-1.3	8%	6.6	33%	32%	15.2
22	13.2%	169	81%	96%	9	6	4	7	-1.2	-3.6	14%	5.0	25%	21%	14
23	16.8%	153	32%	95%	10	5	4	6	-6.8	-8.9	24%	4.5	47%	18%	13.3
24	13.7%	156	92%	97%	9	5	4	7	3.5	-1.9	13%	4.3	67%	49%	13.1
25	13.5%	164	98%	98%	9	6	4	7	1.9	-0.7	11%	5.0	55%	38%	14.2
26	15.9%	151	93%	94%	10	8	6	9	1.8	-0.8	12%	5.2	56%	28%	14.3
27	6.5%	155	96%	93%	10	5.5	4	7	0.9	-2.8	11%	5.1	48%	18%	14.3
28	11.7%	137	86%	95%	9	7	5	8	-1.3	-6.2	19%	6.7	32%	30%	15.3
29	14.0%	115	20%	95%	10	6	5	8	1.6	-2.3	11%	4.4	93%	24%	13.2
30	17.3%	112	96%	95%	10	5	0	6	0.4	-2.8	17%	6.6	82%	39%	10.1
31	7.7%	133	62%	98%	9	6	4	8	3.6	-2.8	13%	6.7	45%	44%	15.2
32	16.4%	96	54%	91%	9	5	3	6	-1.9	-5.1	13%	4.6	58%	30%	13.4

7. Conclusions

The data in these analyses includes patients starting treatment for “wet” NvAMD between 2012 and 2013 from 32 centres with sufficient data for meaningful analysis to be undertaken. There are differences in median baseline VA and age and IMD score between centres. Variation in age and baseline VA may reflect differences in ease of access to specialist treatment centres for NvAMD and will also influence change in visual acuity after the start of treatment. Future comparisons of the outcomes of care between centres will need to take account of these differences in baseline characteristics.

In real-world practice, there is significant variation in follow-up 12 months after the start of treatment and beyond. Increasing age and worse visual acuity at baseline are associated with greater loss to follow-up. There is variation between centres in the regularity of recording of visual acuity. Some of the observed variation may reflect local policies relating to mixed use of paper and electronic records during the study period. Whilst it remains an option to address these differences methodologically through imputation and survival analysis, the disadvantage of such an approach is that it would render the results of the audit less accessible and make interpretation difficult for people not familiar with statistical methodology.

Change in VA from baseline to M12 (adjusted for baseline VA and age) and unadjusted VA change from M3 to M12 each show variation between centres. The percentages of eyes with loss of LogMAR 0.3 or more (≥15 EDTRS letters lost) and with LogMAR 0.3 or better (≥70 letters) at M12 also show variation between centres but these outcomes are expected to be partially dependent on baseline VA.

Within the data extraction, it was not possible to directly identify delays in follow-up, although this may be possible in future data extractions as the Medisoft EMR includes functionality to collect information on the intended review period. Of relevance is the fact that there is variation between centres in the time taken to complete the loading phase of three initial monthly injections. Delay in achieving the three loading phase injections suggests that there may not be robust pathways or sufficient capacity to meet demand in some centres with a clear implication that delays to appointments were occurring. Prompt initiation of treatment followed by regular assessments and timely maintenance treatment is essential to maintenance of vision.

There are concerns that the accurate identification of cases of presumed infectious endophthalmitis after intra-vitreal injection may not be possible. Although the incidence figures for all 32 centres may be higher than expected, the number of cases is too low for meaningful inter-centre comparison.

8. Feasibility of an AMD National Audit

Prompt initial and timely ongoing treatment for NvAMD has the potential to preserve the sight of many thousands of patients who may otherwise end up blind and dependent on individuals and the state for support. With 39,700 new cases per year in the UK (projected to rise by a third by 2020), an annual drugs cost for treatment of NvAMD estimated to be the greater part of £450 million, and 75,000 AMD hospital visits annually (in England alone) this treatable condition, currently the most common cause of permanent blindness, stands out as a candidate for a national audit of process and outcomes.

This analysis suggests that it would be possible to undertake a national audit of treatment for "wet" NvAMD. A prerequisite would be the provision of data collection tools for currently paper based centres in a similar way to the method employed for collection of cataract surgery data where audit tools were provided in the form of a specialist EMR module and a template conforming to the national minimum cataract dataset. The time frame for a NvAMD audit would be longer than for cataract. From initiation of audit data collection there would be a necessary period to accumulate sufficient patients in each centre to make comparative analysis meaningful, following which the most recently included patients would need a 12 month minimum follow-up period to determine outcomes and patterns of care. Separate reporting of first and second treated eyes would be needed for a full national audit, a mature audit with good data collection could be extended beyond 12 months without additional complexities. Inclusion of the "dry" form of AMD would be impractical because these patients are frequently only seen once and then discharged which means that information on disease severity would be lacking as disease progression is not tracked and recorded.

The primary outcomes proposed here relate to preservation of vision through timely intravitreal injection treatments for NvAMD. The three primary outcomes for the 32 centres for preservation of vision are summarised in Figure 7 and Figure 8, with timeliness of treatment in Figure 9 and Table 2. In this analysis the proportion of patients receiving three injections within three months of presentation (timely treatment) has been used as a primary process measure. An alternative process measure that was considered, was the number of injections in the first year after initiation of treatment, for which data are available. The stakeholders however indicated a clear wish for delay to follow-up to be used as a process measure but the data in the current extract did not include this information. The Medisoft EMR does provide functionality for recording this information so provided this information is being recorded it may in future be possible for delays to appointments to be included as a process measure.

The validity of these results depends on data completeness and accuracy. Data completeness varies between centres and reasons for loss to follow-up are currently unknown. Approximately two thirds of the 32 centres analysed had follow-up data of up to one year for 85% or more of patients. A Section 251 exemption enabled national audit would allow identification of patients lost to follow resulting from death, which in this elderly age group would be expected to be around 5% per year (estimate derived from separate data). In view of the issues identified in regard to losses to follow-up, data completeness would need to form an outcome in its own right and should capture reasons for loss to follow-up (e.g. failure of treatment, patient deciding against further treatment, death etc.) The EMR includes functionality to record this information so that where either a clinician or a patient makes an active decision to discontinue treatment it would be possible for this to be captured. Two of the three secondary outcomes were found to be feasible. The third secondary outcome could be substituted with an alternative 'safety metric' of severe vision loss (e.g. VA loss ≥0.6 LogMAR or 30 ETDRS letters) in the treated eye, data for which would be readily available.

This study has demonstrated the feasibility of a national audit of NvAMD treatment with important variations between centres having been identified. Upscaling the current exercise to a national audit of NvAMD would provide the necessary levers for improving standards of care in this common blinding condition, the success of which relies on prompt diagnosis, rapid initiation of treatment and ongoing, timely maintenance therapy over several years to preserve visual function. Expected demographic changes predict that the NHS cost and treatment burden to the NHS will continue to increase in the forseeable future.

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It is with deep regret that we note the death of our friend and colleague Robert Johnston, who sadly died in September 2016. Without his inspirational vision, determination and career long commitment to quality improvement in ophthalmology this work would not have been possible.

Appendix 1. Candidate Outcome Metrics for consideration harvested from Stakeholder Group Discussion

Aspects of service of potential interest as outcomes

- High level overview items
    - Median VA at presentation; M3; M12 and M24.
    - % Eyes with LogMAR ≥ 0.3 (70 ETDRS letters) at baseline; M3; M12 and M24
- Measures of Access to services
    - Baseline Median VA
        - First and second eyes separately
        - If both treated on same day, then worse = first (if = spin coin)
- Measures of Treatment Effectiveness
    - Median VA change from baseline to M12 and M24
        - Losses to follow-up also as %
        - Last observation carried forward (LOCF)
        - Imputation for missing data
        - Adjusted for Baseline VA and Age
        - First and second eyes separately
- Measures of Safety
    - Endophthalmitis Incidence rate
        - Data search strategies needed for detection of this event
        - Accept limitation on case ascertainment so 'minimum incidence' reported if feasible
        - Issues with possible repeated episodes (acknowledged as rare)
    - % With severe VA Loss ≥0.6 LogMAR or 30 ETDRS letters
        - First and second eyes separately
- Measures HES workload burden
    - Mean number of visits / year (patients)
    - Mean number injections / year (eyes)
- Measures of process
    - Follow-up delays - difference between planned and actual follow-up date

The longer list of candidate metrics was refined by an expert group using email discussion. By prioritising perceived importance of candidate metrics a short list of six metrics resulted which were taken forward for feasibility assessment based on the available data.

Short list of Candidate Outcome Metrics

1. Primary effectiveness or "good" outcome
    a. Visual acuity change from baseline to month 12, adjusted for starting acuity and age
2. Primary failure or "bad" outcome
    a. Percentage of eyes losing LogMAR VA 0.3 or worse, or 15 letters or more (experiencing moderate or worse visual loss) between baseline and month 12 (with or without a survival analysis graphical KM plot)
3. Primary "process" outcome
    a. In the absence of follow-up delay data the time for given percentages to complete the loading phase of three monthly injections per centre (with or without a survival analysis and graphical KM plot) was proposed.
4. Secondary effectiveness or "good" outcomes
    a. VA change from M3 to M12 and/or M24 (NOT adjusted for baseline VA. Loss to follow-up an issue particularly beyond 12 months)
    b. Percentage of eyes maintaining acuity LogMAR 0.3 (70 ETDRS letters) of better at M12 and/or M24, with and/or without adjustment for baseline acuity (with or without a survival analysis and graphical KM plot).
5. Secondary "bad" outcome
    a. Complications – endophthalmitis incidence rate
        i. The data would be of limited value if reported by individual year
        ii. There is likely to be significant under-reporting and difficult case ascertainment.
        iii. There would be no way of distinguishing between culture positive and negative cases.

Acknowledgement

The RCOphth National Audit group are grateful to all those colleagues who contributed to the stakeholder exercise which has strengthened this feasibility study.

Appendix 2. Conversions from LogMAR to ETDRS Letter along with approximate Snellen equivalents

The LogMAR score is reversed in comparison with the number of letters read so that the better the VA the smaller is the LogMAR score.

LogMAR	Letters	Snellen
-0.3	100	6/3
-0.2	95	6/4
-0.1	90	6/5
0.0	85	6/6
0.1	80	6/8
0.2	75	6/10
0.3	70	6/12
0.4	65	6/15
0.5	60	6/19
0.6	55	6/24
0.7	50	6/30
0.8	45	6/38
0.9	40	6/48
1.0	35	6/60
1.1	30	4.7/60
1.2	25	3.8/60
1.3	20	3/60
1.4	15	2.4/60
1.5	10	1.9/60
1.6	5	1.5/60
1.7	0	1.2/60
1.8		1/60
1.9		1/79
2.0		1/100
2.1	CF	0.5/60
2.2		0.5/80
2.3		0.5/100
2.4	HM	0.5/120
2.5		0.5/160
2.6		0.5/200
2.7	PL	0.5/240
2.8		0.5/320
2.9		0.5/400
3.0	NPL	0.5/480

Appendix 3. Glossary and Abbreviations

Abbreviation	Description
%	Percentage
<	Less than
>	Greater than
AMD	Age-related macular degeneration
CF	The ability to count fingers
COP	Consultant Outcomes Publication
EMR	Electronic Medical Record
ETDRS	Early Treatment Diabetic Retinopathy Study
HES	Hospital Episode Statistics
HM	The ability to distinguish hand movements
HQIP	Healthcare Quality Improvement Partnership
ICHOM	The International Consortium for Health Outcomes Measurement
IMD	Index of Multiple Deprivation
IQR	Interquartile Range
LOCF	Last observation carried forward
LogMAR	An eye chart comprising of rows of letters which can be used to estimate visual acuity
M3	Month three
M12	Month 12
M24	Month 24
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NOD	National Ophthalmology Database
NPL	No perception of light
NvAMD	Neovascular Age-related macular degeneration
P value	Significance level
PL	Perception light
PPI	Patient and Public Involvement
PROM	Patient Reported Outcome Measures

R^2	Percentage of variance explained
S251 exemption	Approval for exemption from section 251 of the NHS Health and Social Care Act 2006 which allows for certain uses of patient identifiable data
Snellen	An eye chart that can be used to measure visual acuity
VA	Visual Acuity

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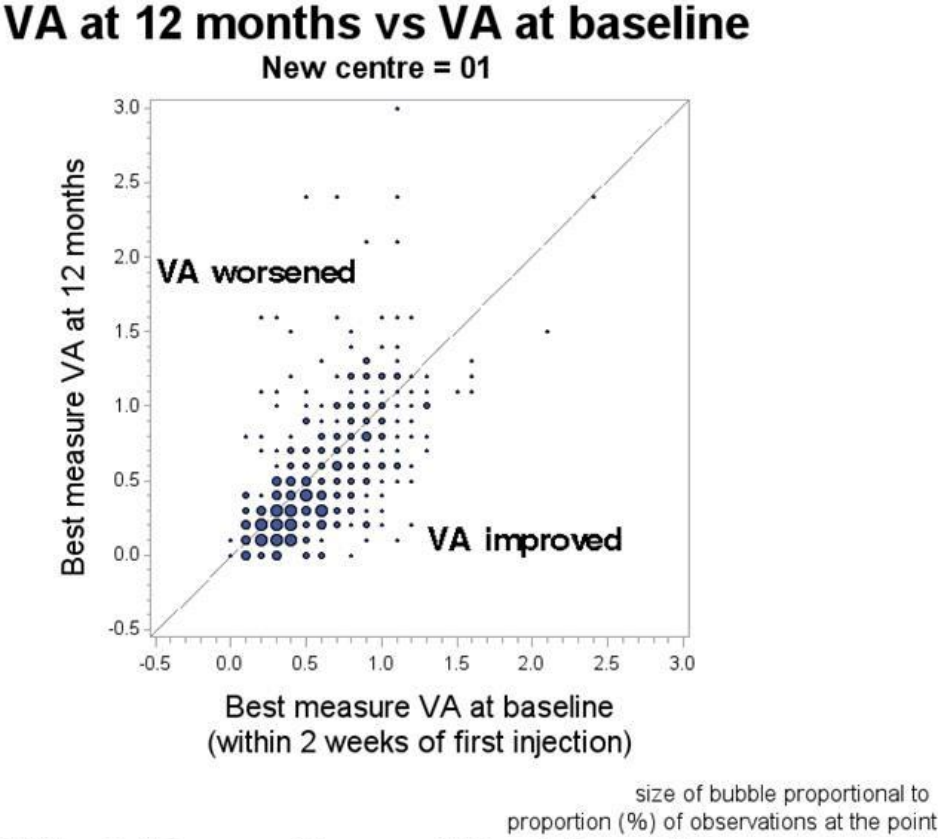
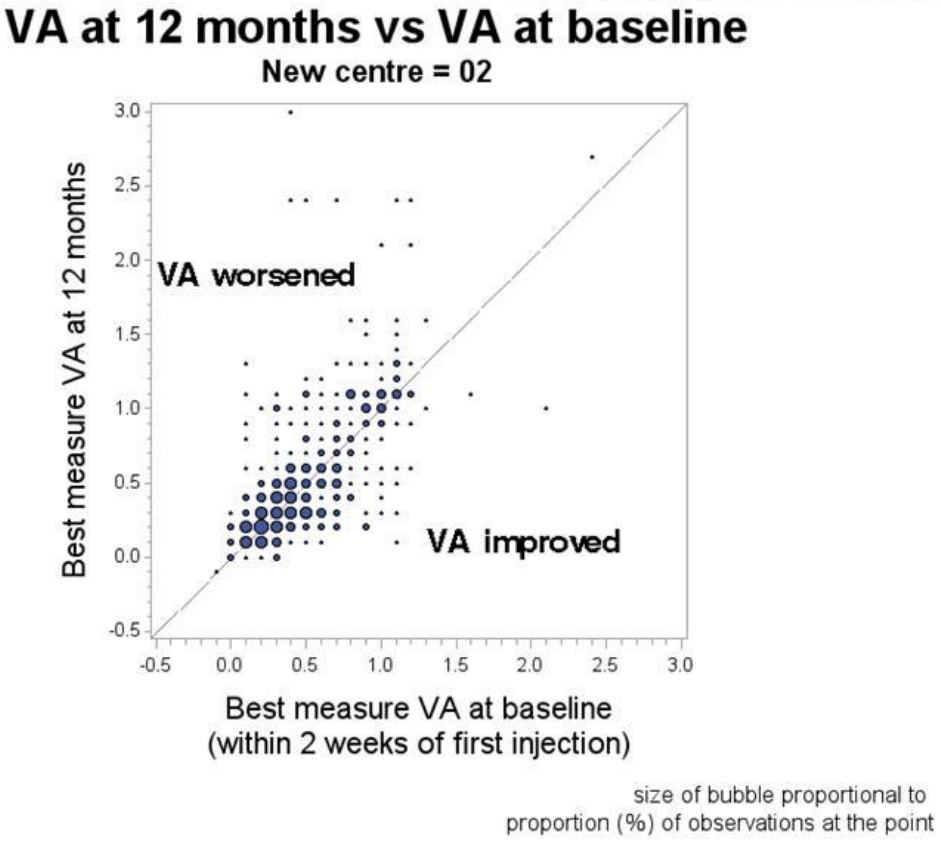
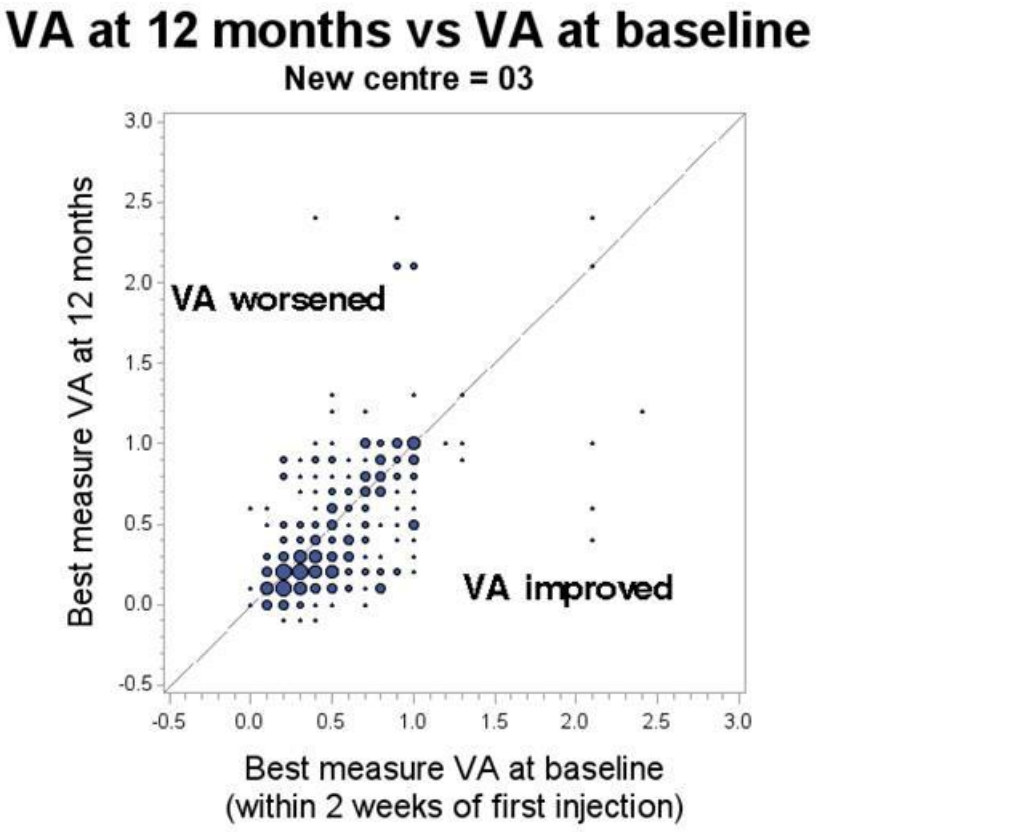
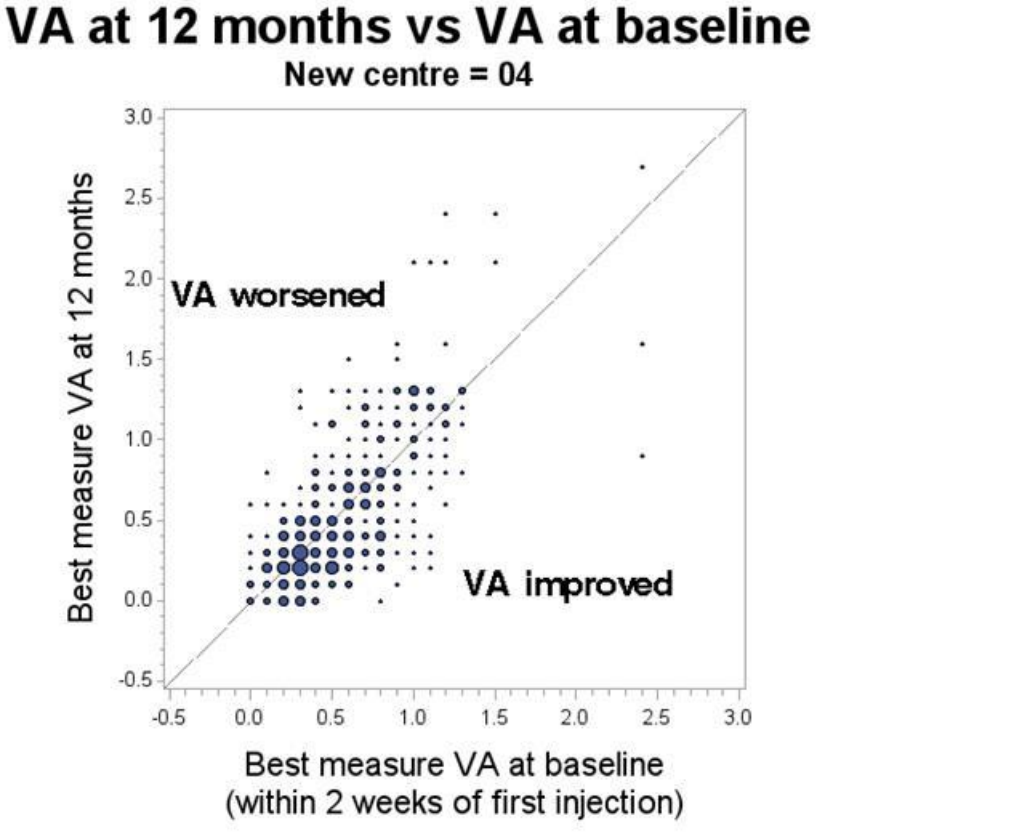
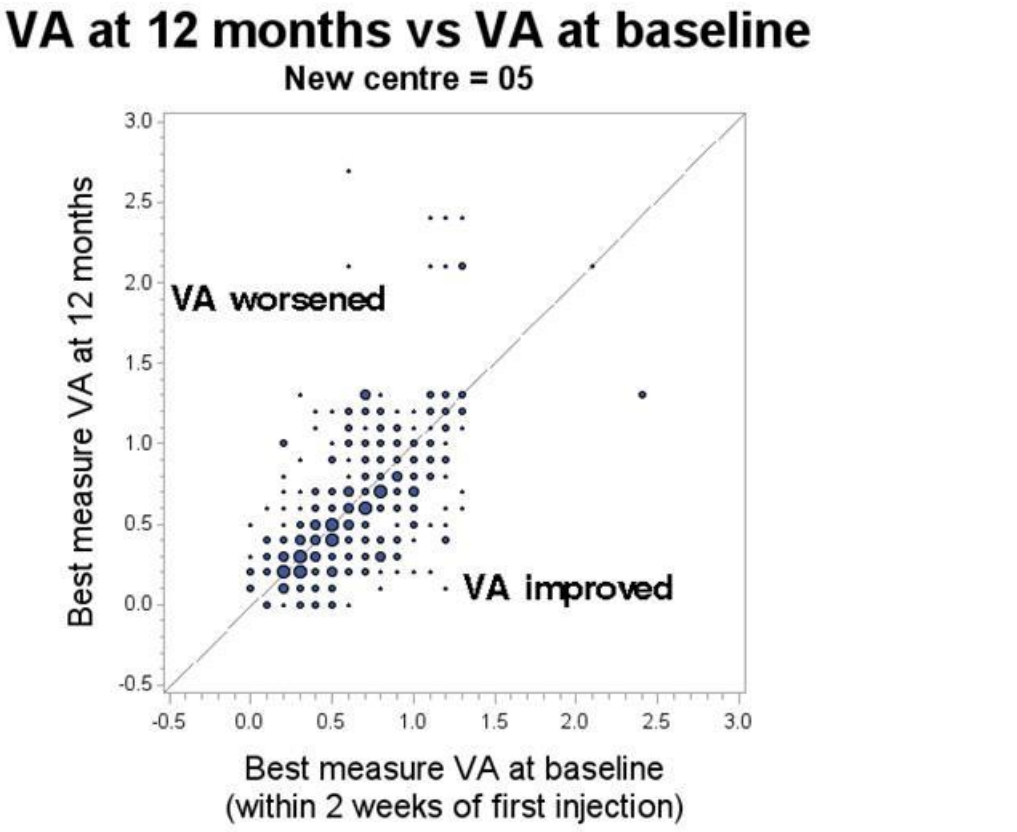
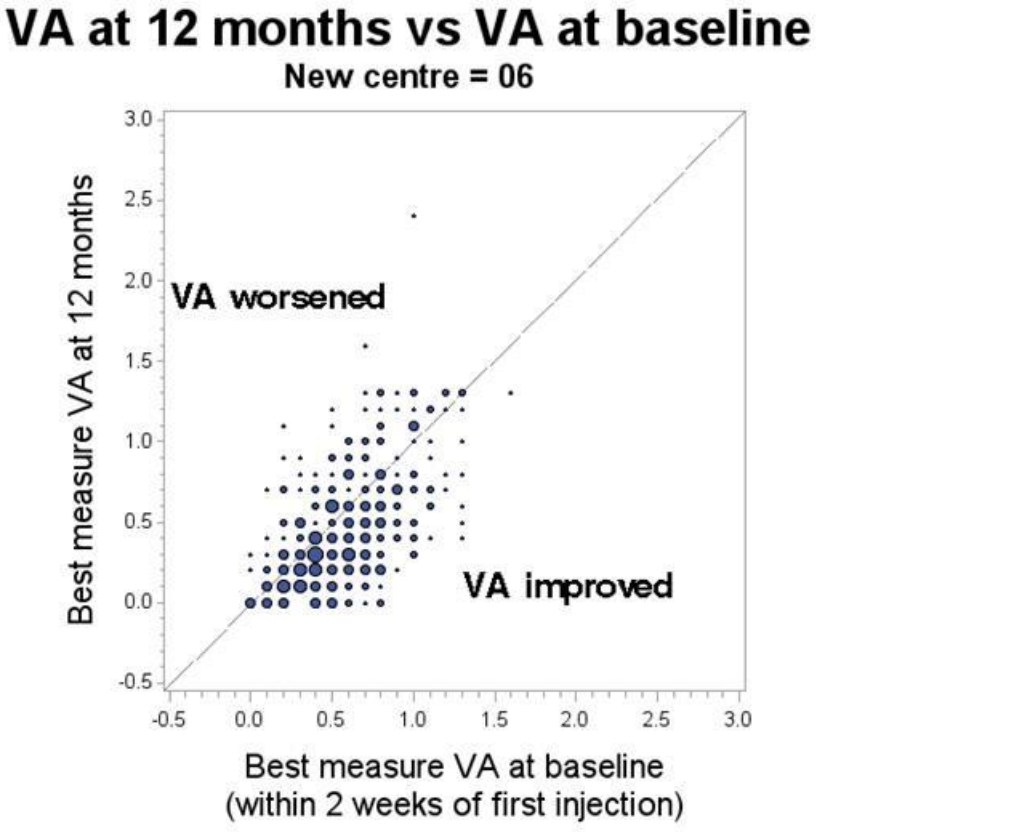


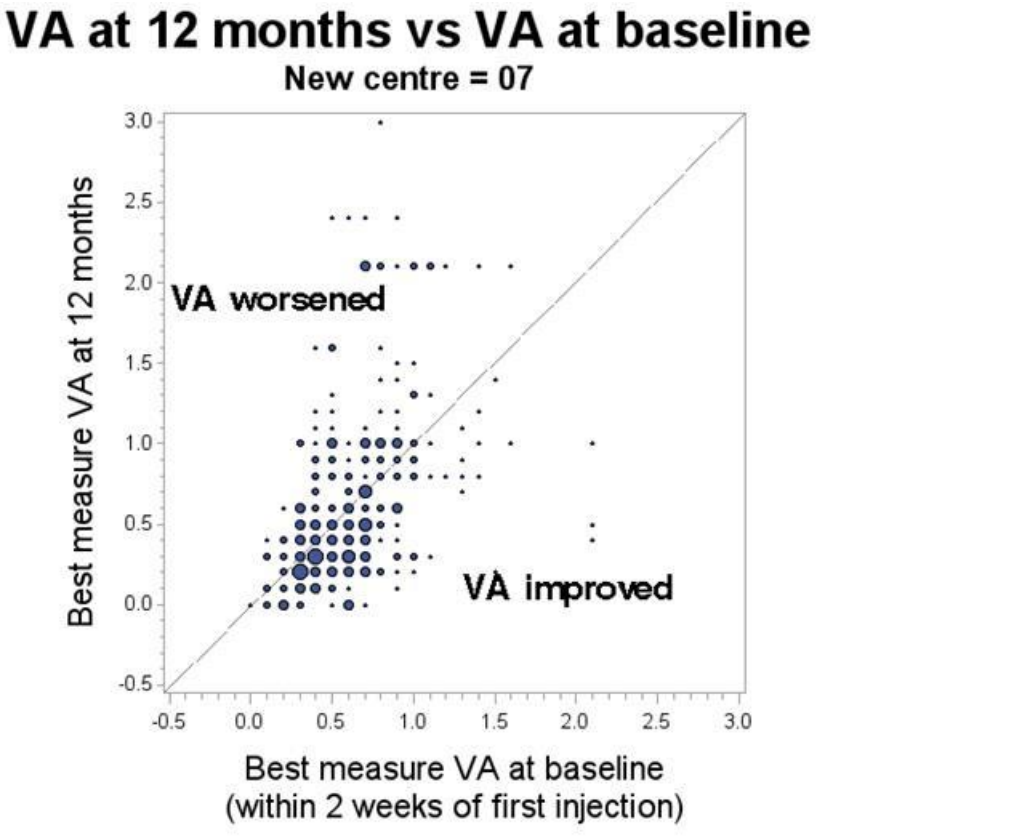


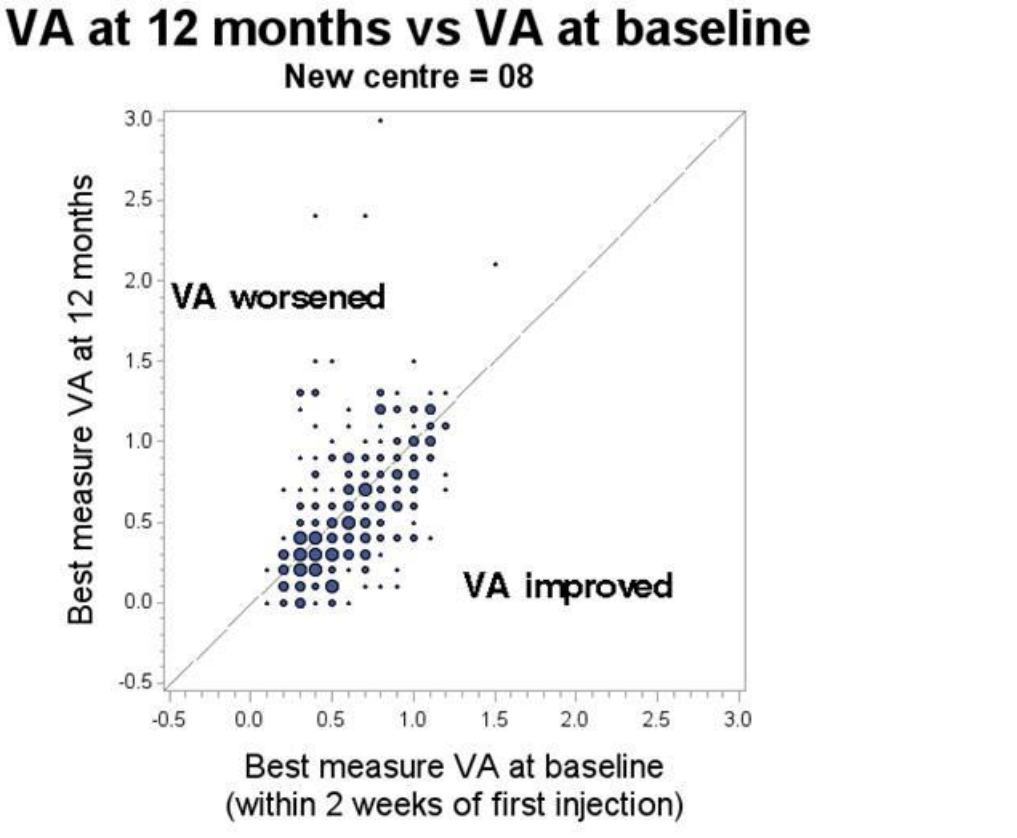

VA at 12 months vs VA at baseline
New centre = 03
Best measure VA at 12 months
VA worsened
VA improved
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

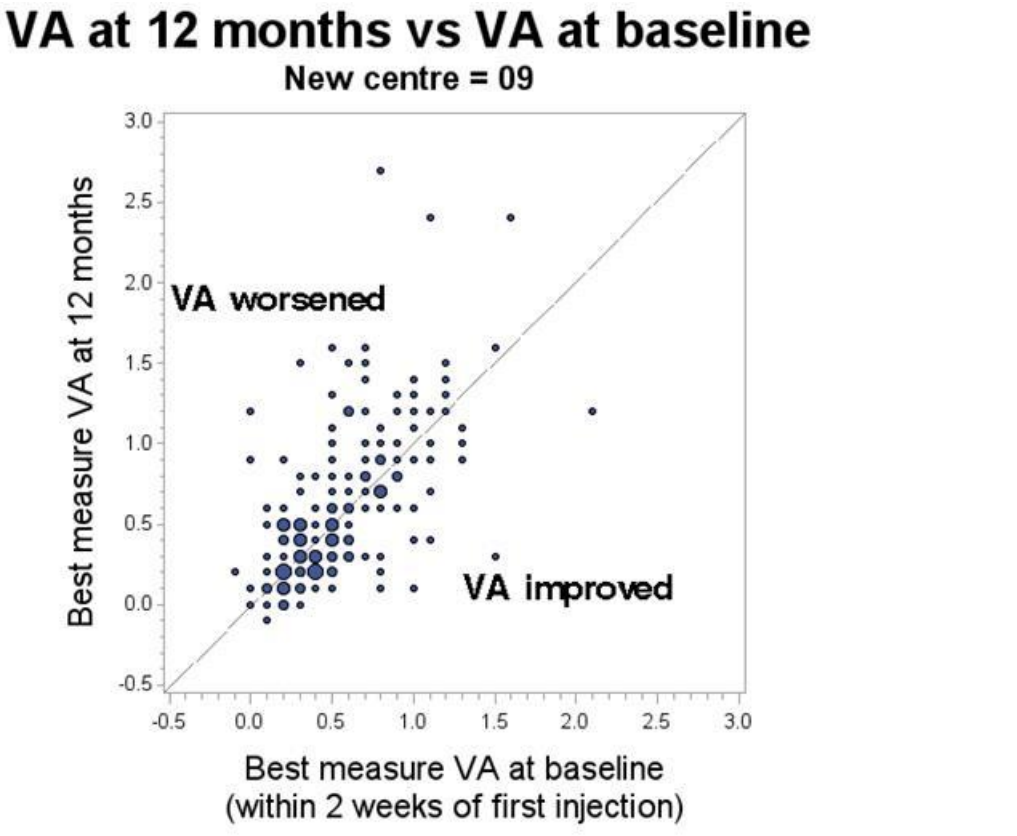

VA at 12 months vs VA at baseline
New centre = 04
Best measure VA at 12 months
VA worsened
VA improved
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

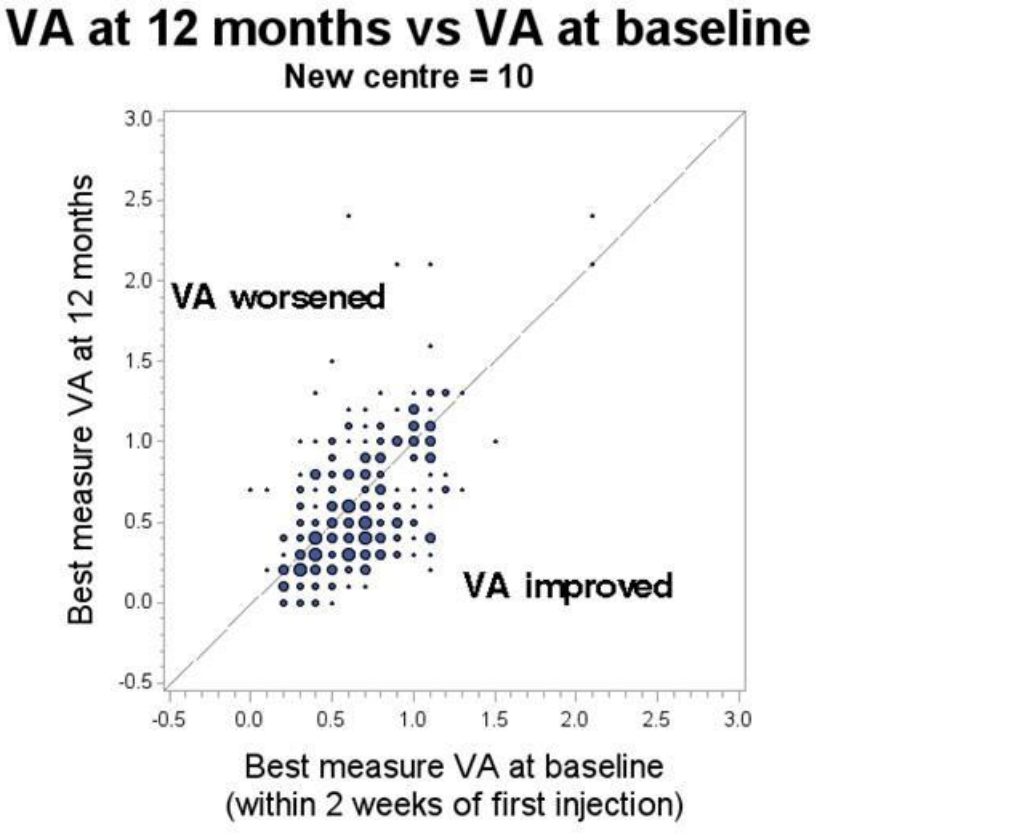

VA at 12 months vs VA at baseline
New centre = 05
Best measure VA at 12 months
VA worsened
VA improved
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

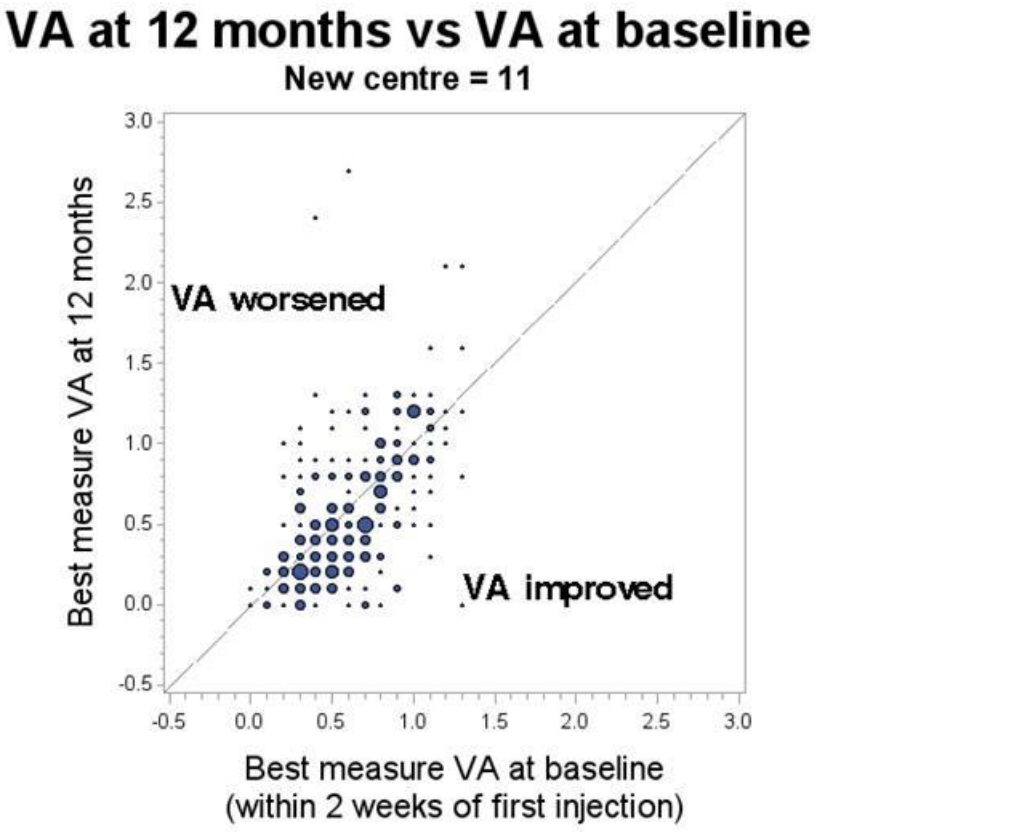

VA at 12 months vs VA at baseline
New centre = 06
Best measure VA at 12 months
VA worsened
VA improved
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

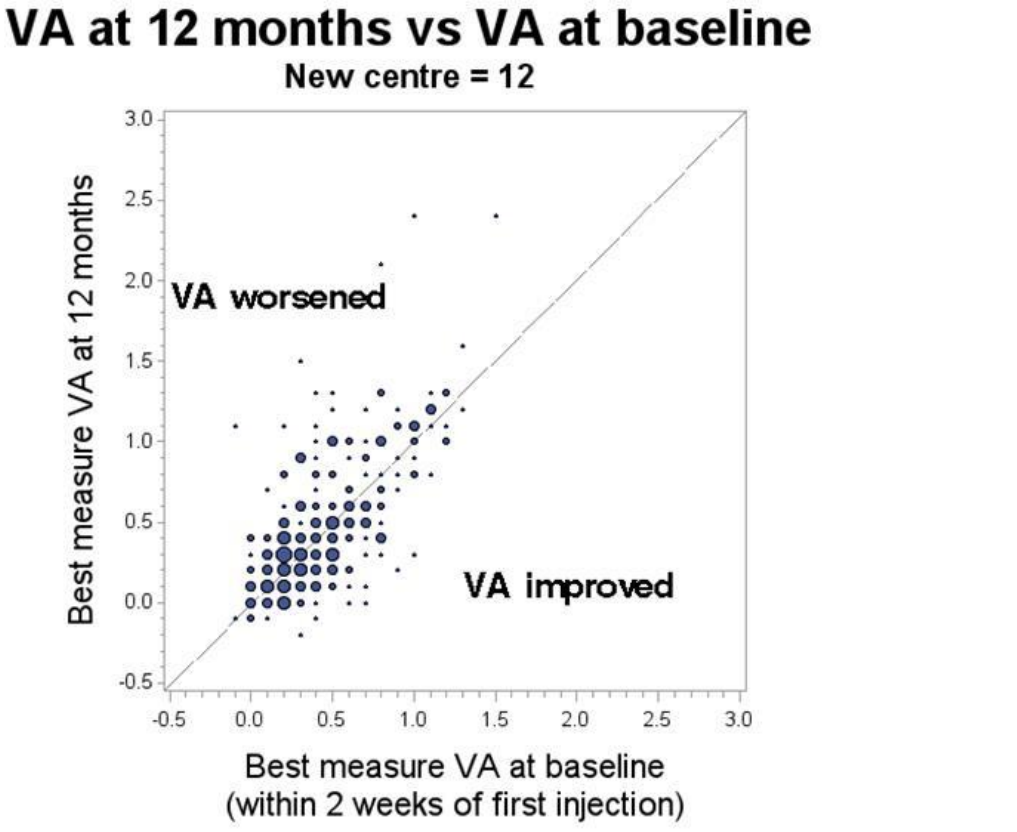

VA at 12 months vs VA at baseline
New centre = 07
Best measure VA at 12 months
VA worsened
VA improved
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

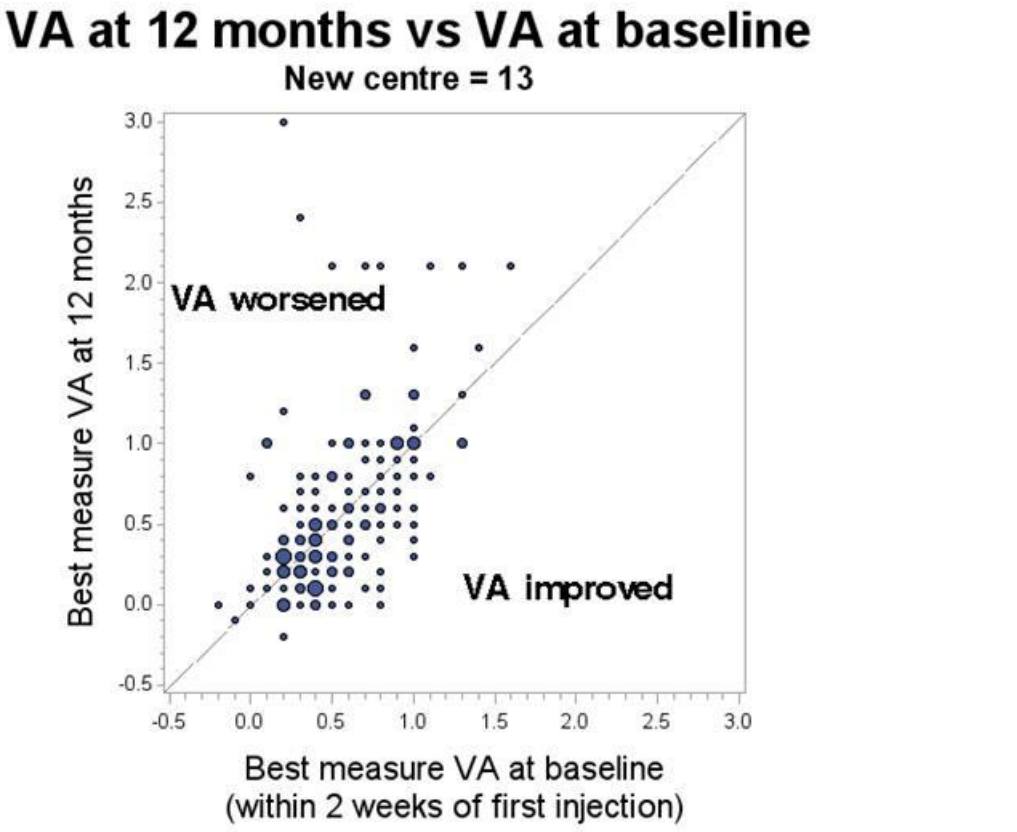

VA at 12 months vs VA at baseline
New centre = 08
Best measure VA at 12 months
VA worsened
VA improved
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

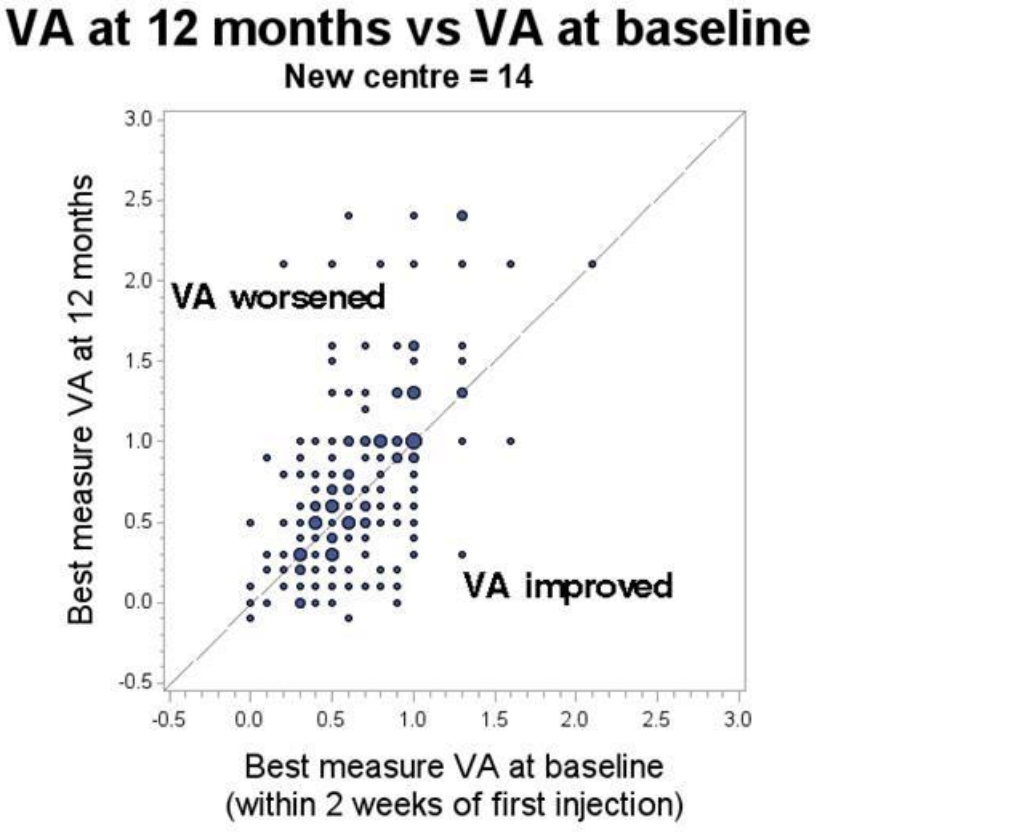

VA at 12 months vs VA at baseline
New centre = 09
Best measure VA at 12 months
VA worsened
VA improved
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

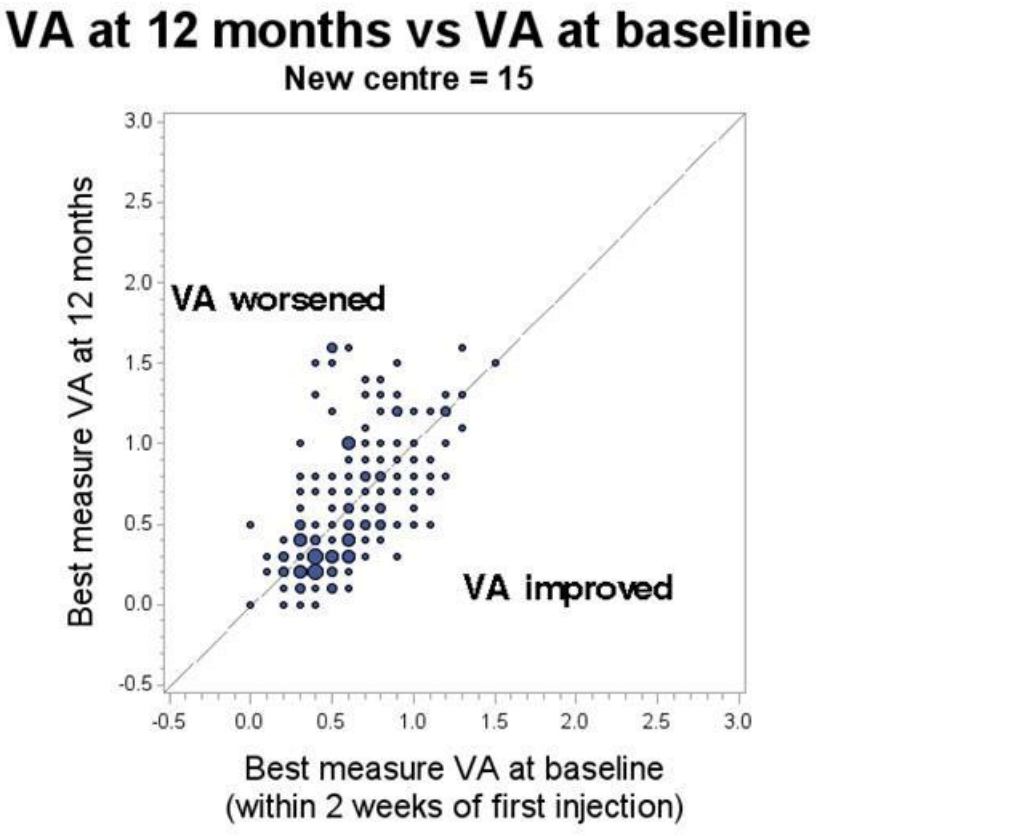

VA at 12 months vs VA at baseline
New centre = 10
Best measure VA at 12 months
VA worsened
VA improved
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

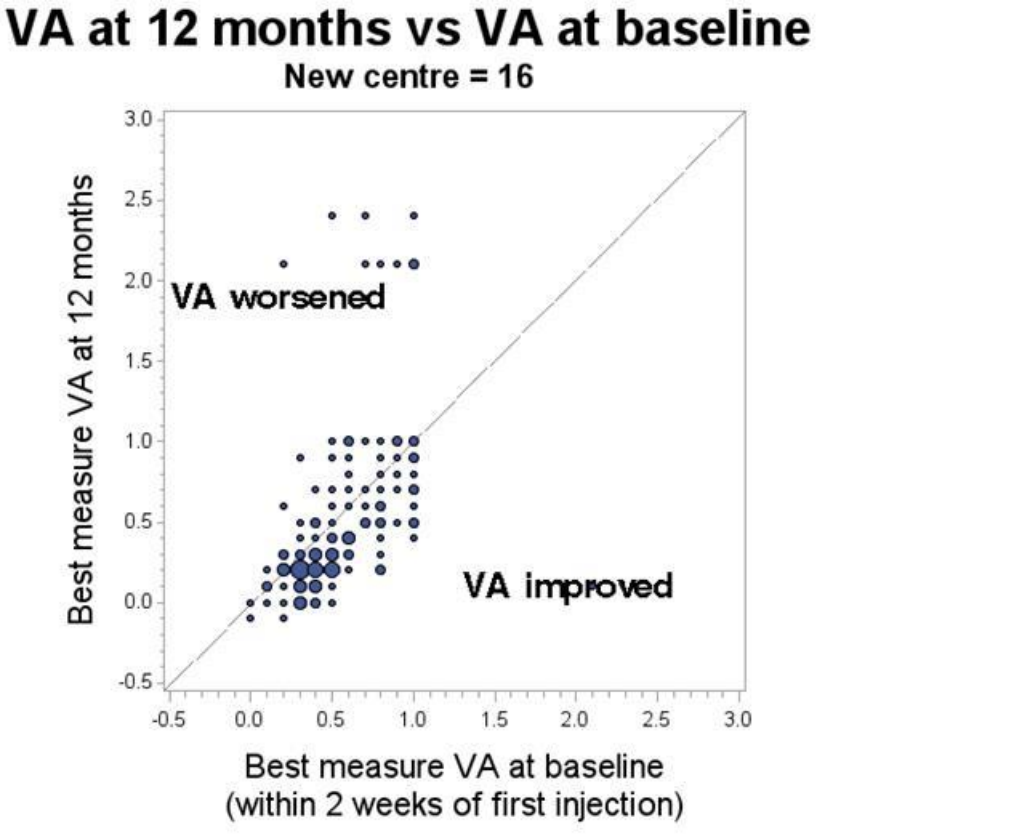

VA at 12 months vs VA at baseline
New centre = 11
Best measure VA at 12 months
VA worsened
VA improved
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

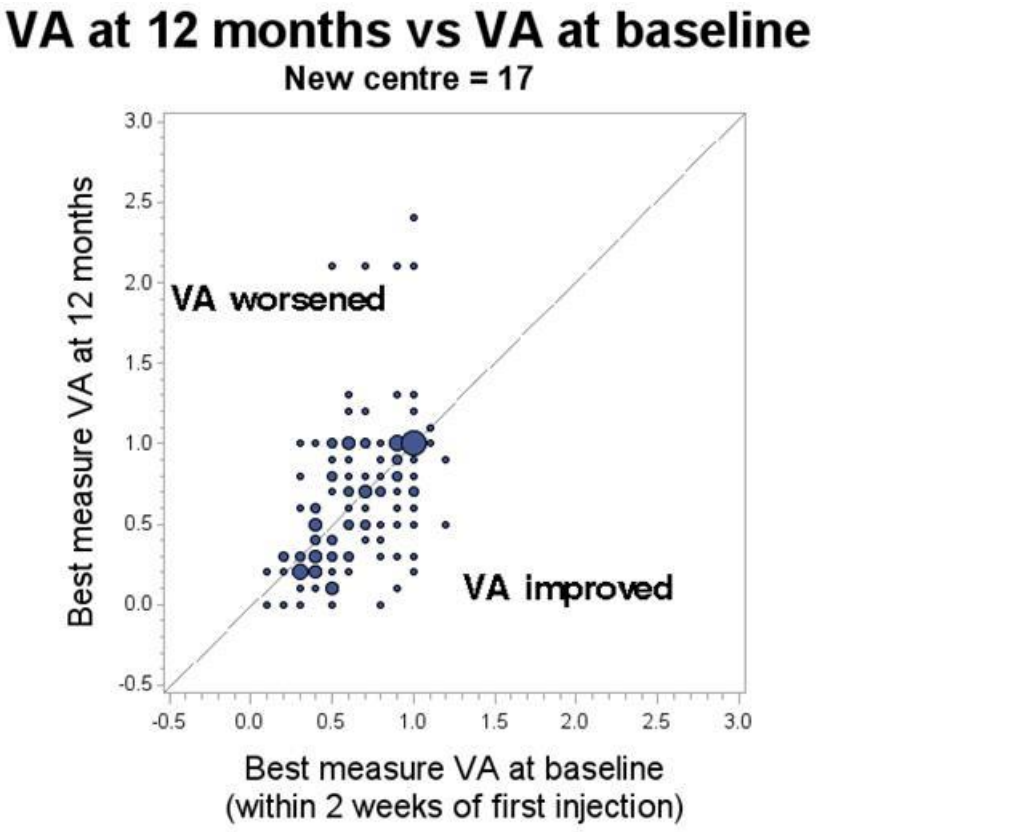

VA at 12 months vs VA at baseline
New centre = 12
Best measure VA at 12 months
VA worsened
VA improved
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

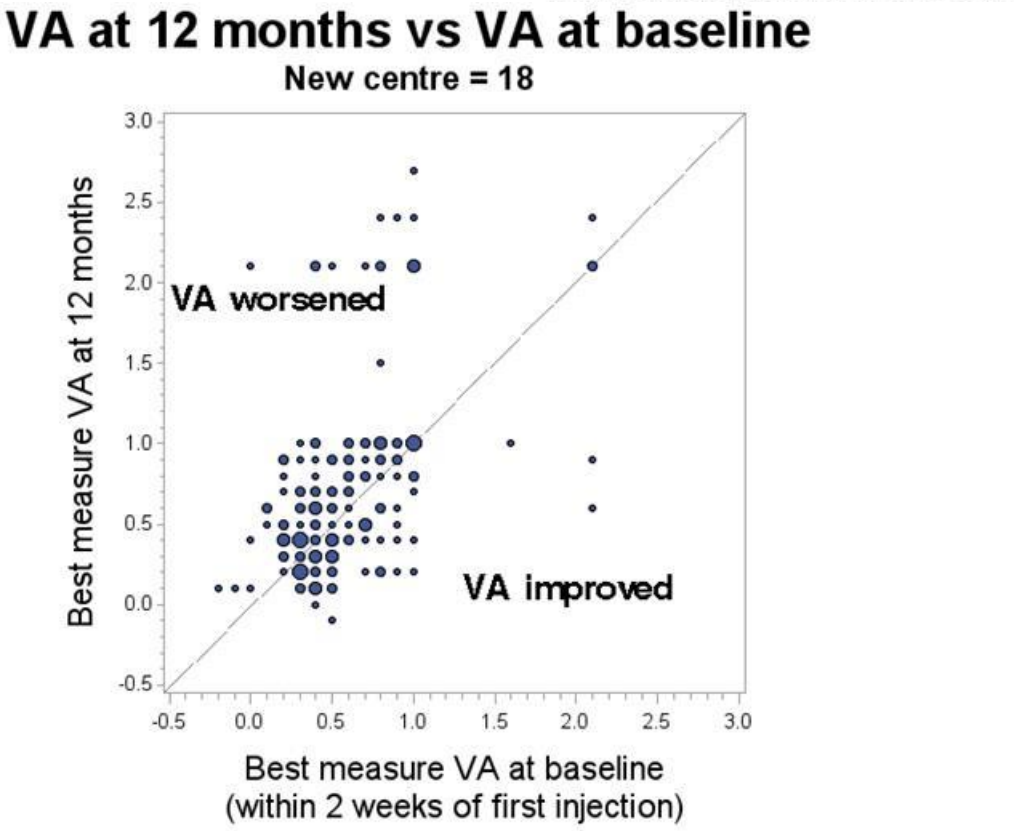

VA at 12 months vs VA at baseline
New centre = 13
Best measure VA at 12 months
VA worsened
VA improved
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

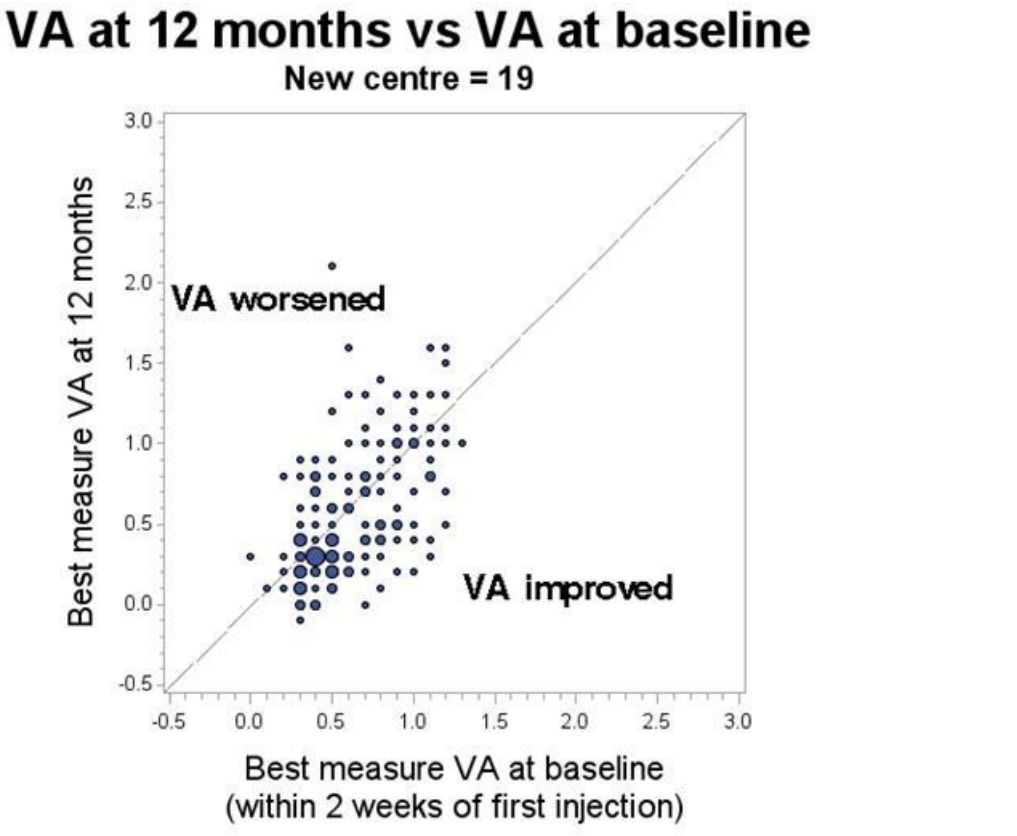

VA at 12 months vs VA at baseline
New centre = 14
Best measure VA at 12 months
VA worsened
VA improved
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

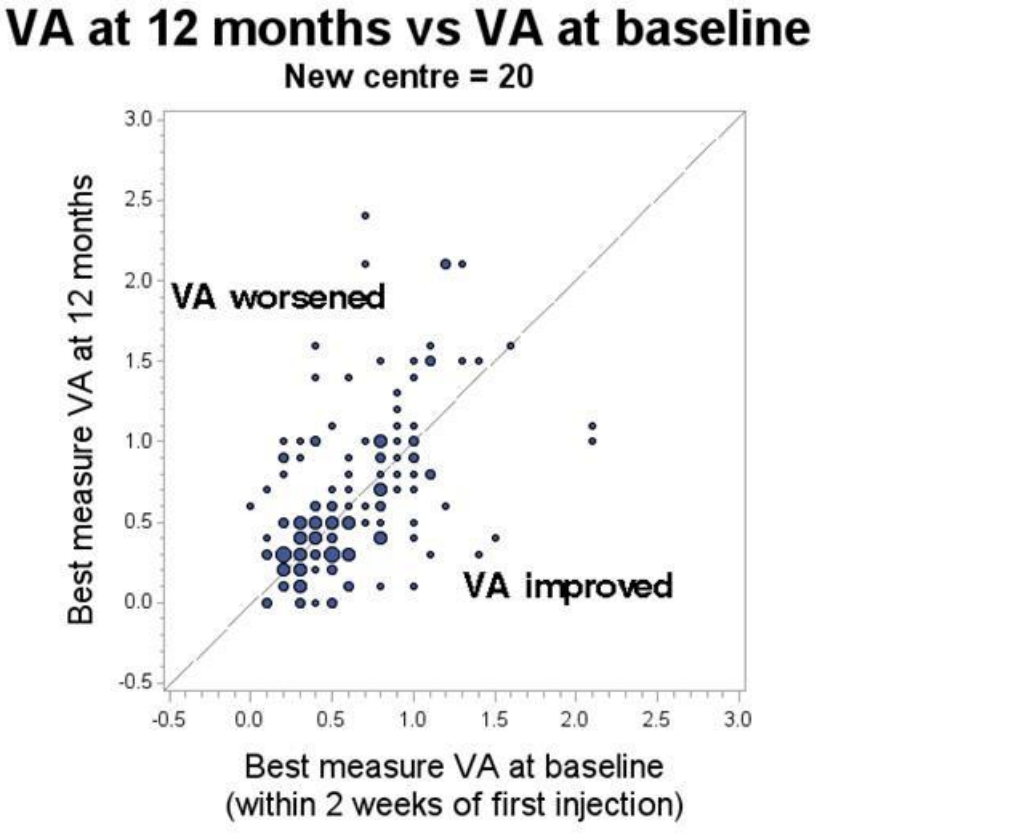

VA at 12 months vs VA at baseline
New centre = 15
Best measure VA at 12 months
VA worsened
VA improved
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

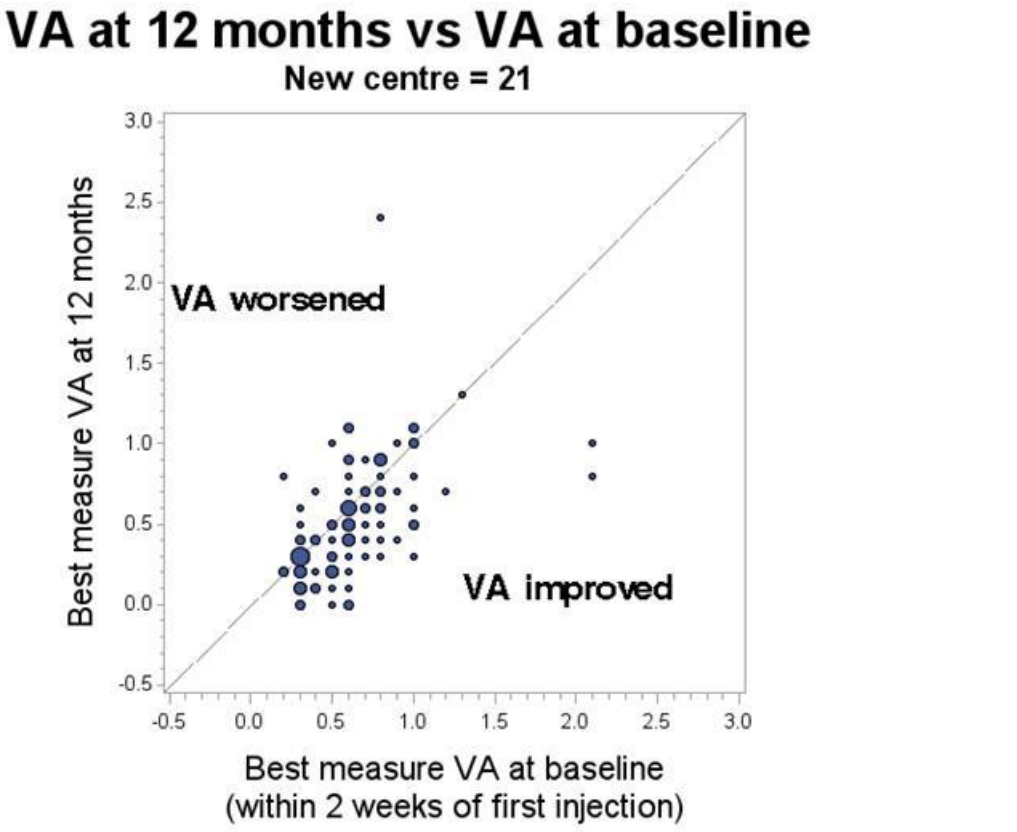

VA at 12 months vs VA at baseline
New centre = 16
Best measure VA at 12 months
VA worsened
VA improved
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

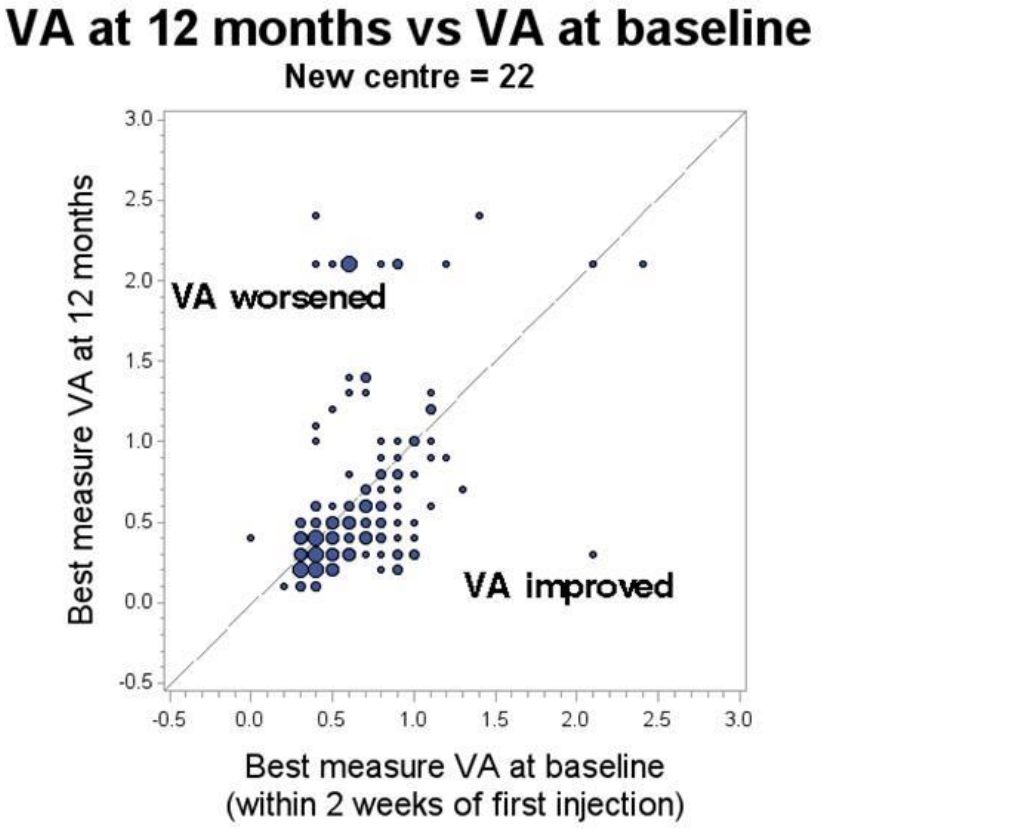

VA at 12 months vs VA at baseline
New centre = 17
Best measure VA at 12 months
VA worsened
VA improved
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

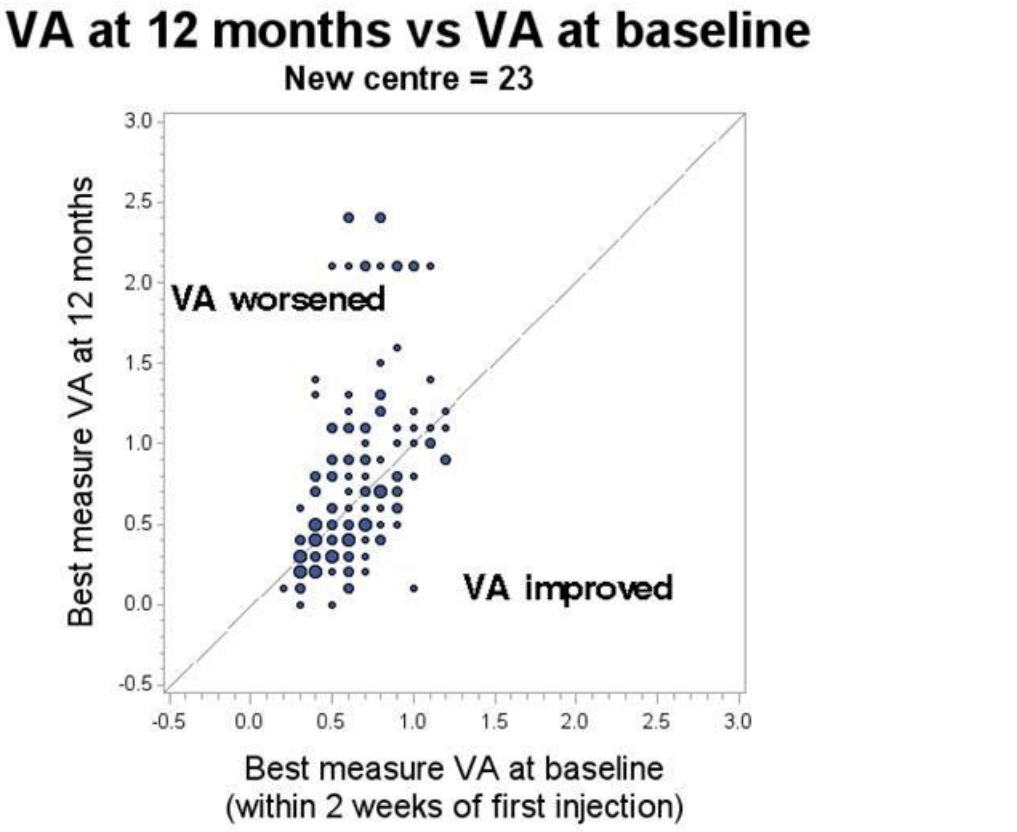

VA at 12 months vs VA at baseline
New centre = 18
Best measure VA at 12 months
VA worsened
VA improved
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

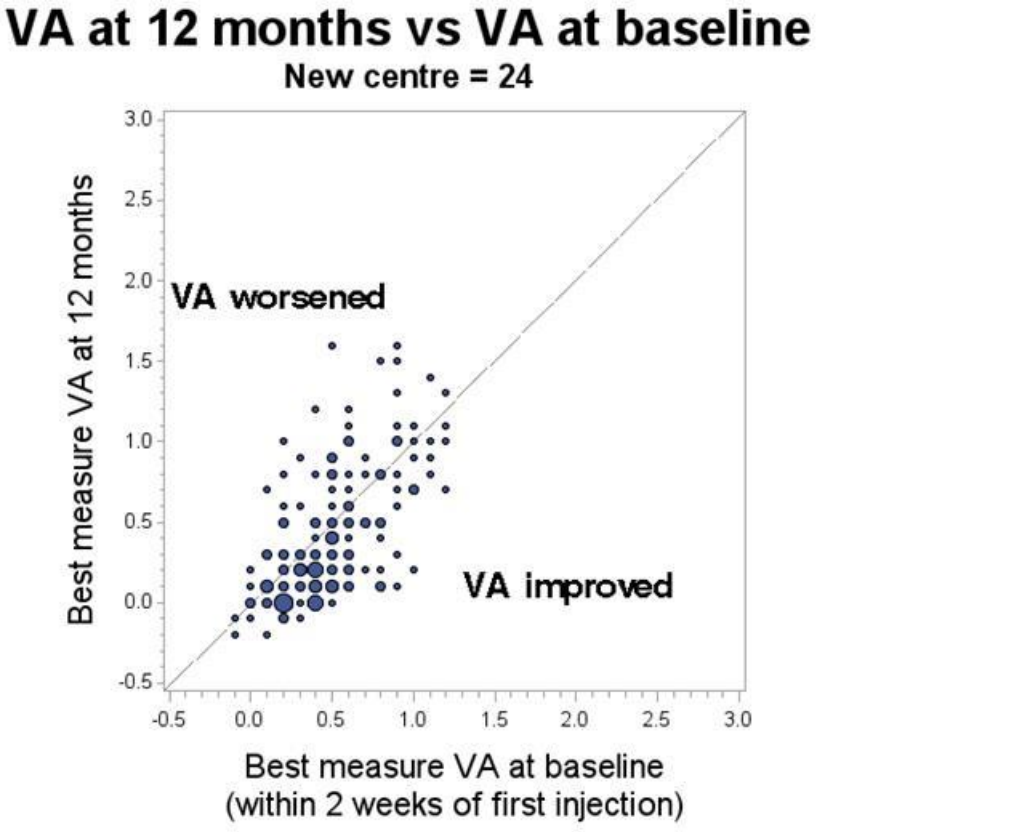

VA at 12 months vs VA at baseline
New centre = 19
Best measure VA at 12 months
VA worsened
VA improved
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

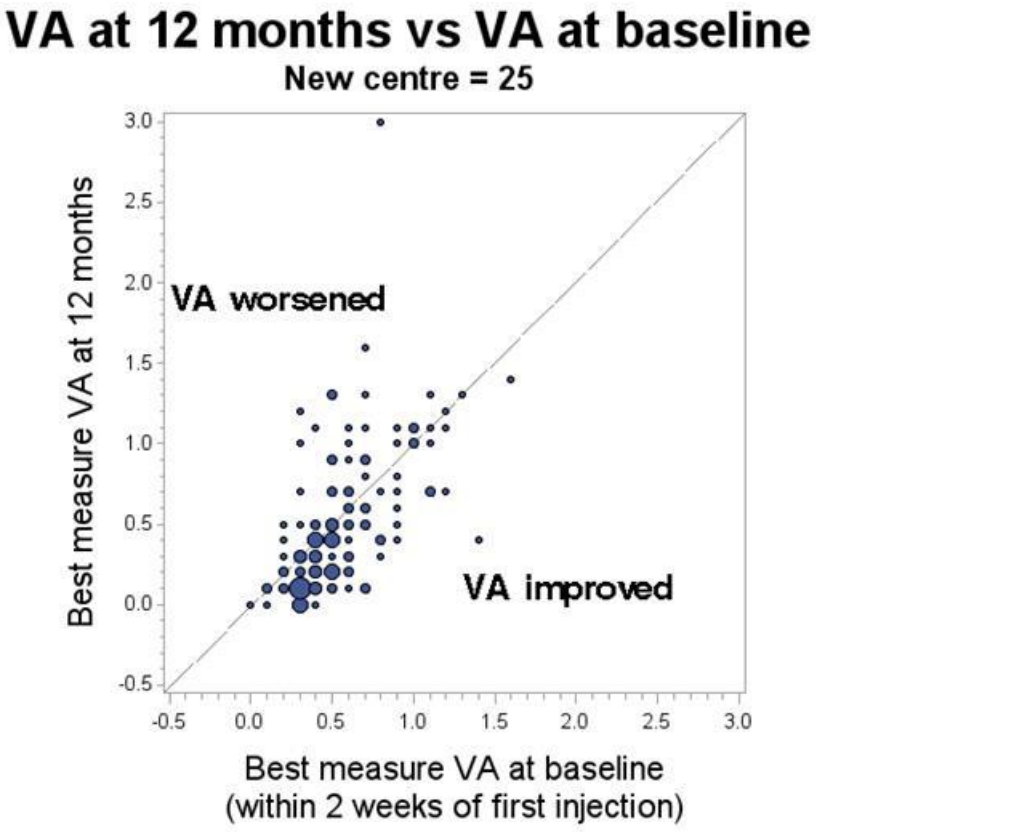

VA at 12 months vs VA at baseline
New centre = 20
Best measure VA at 12 months
VA worsened
VA improved
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

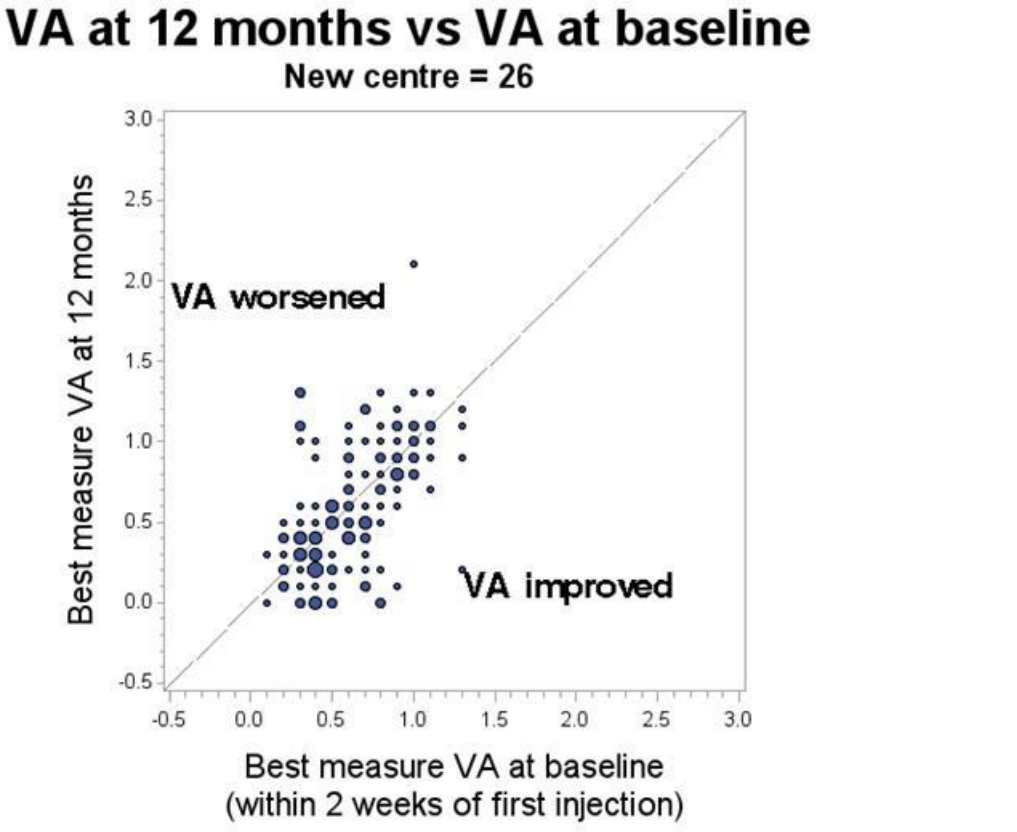

VA at 12 months vs VA at baseline
New centre = 21
Best measure VA at 12 months
VA worsened
VA improved
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

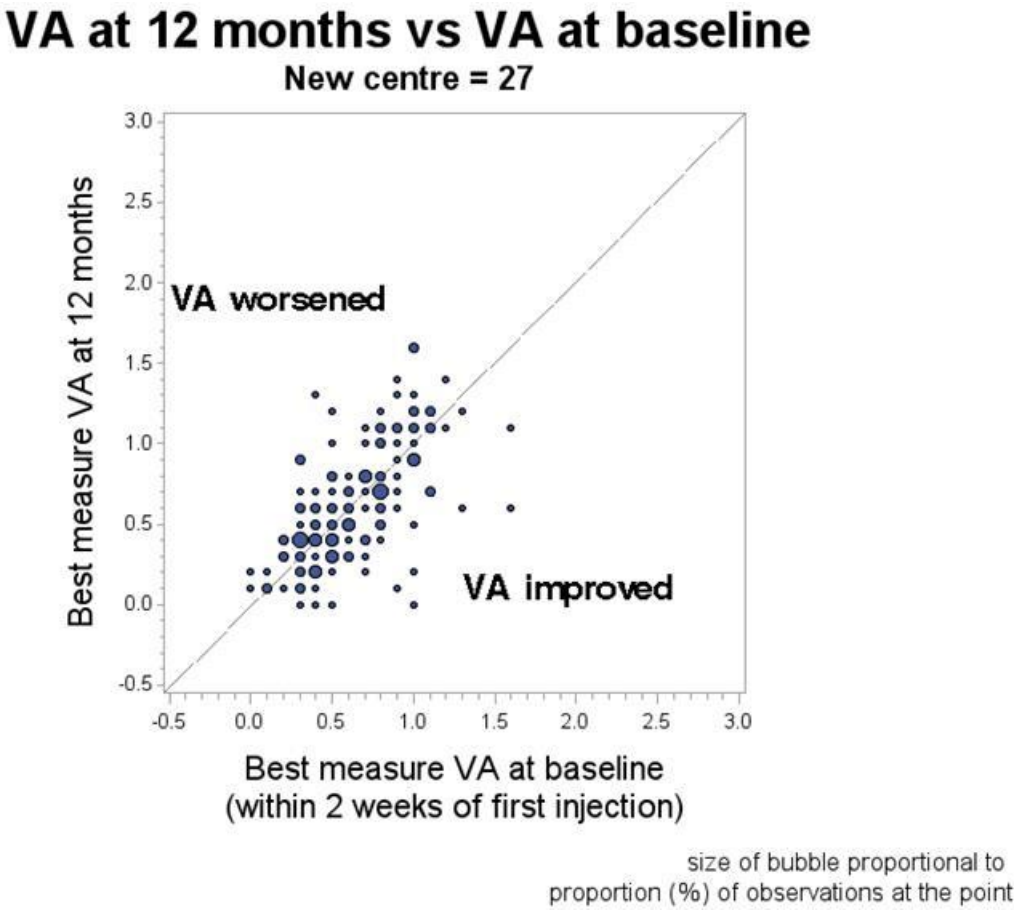

VA at 12 months vs VA at baseline
New centre = 22
Best measure VA at 12 months
VA worsened
VA improved
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

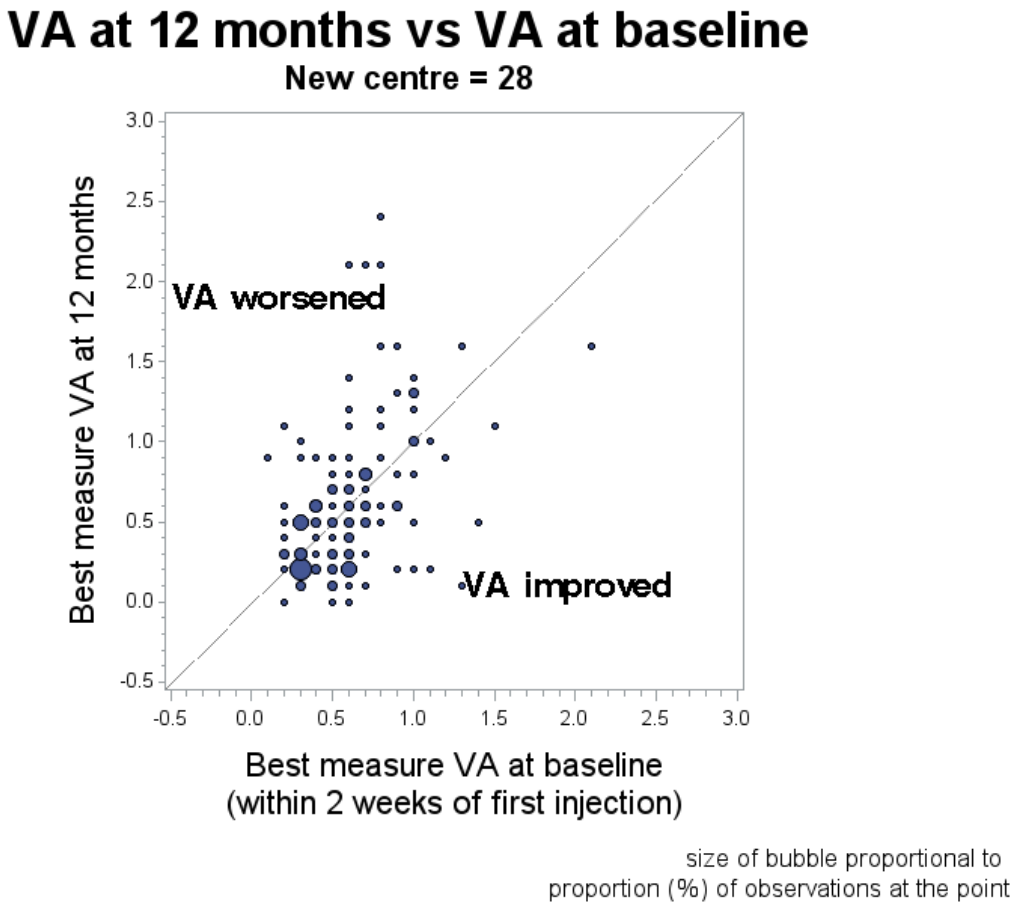

VA at 12 months vs VA at baseline
New centre = 23
Best measure VA at 12 months
VA worsened
VA improved
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

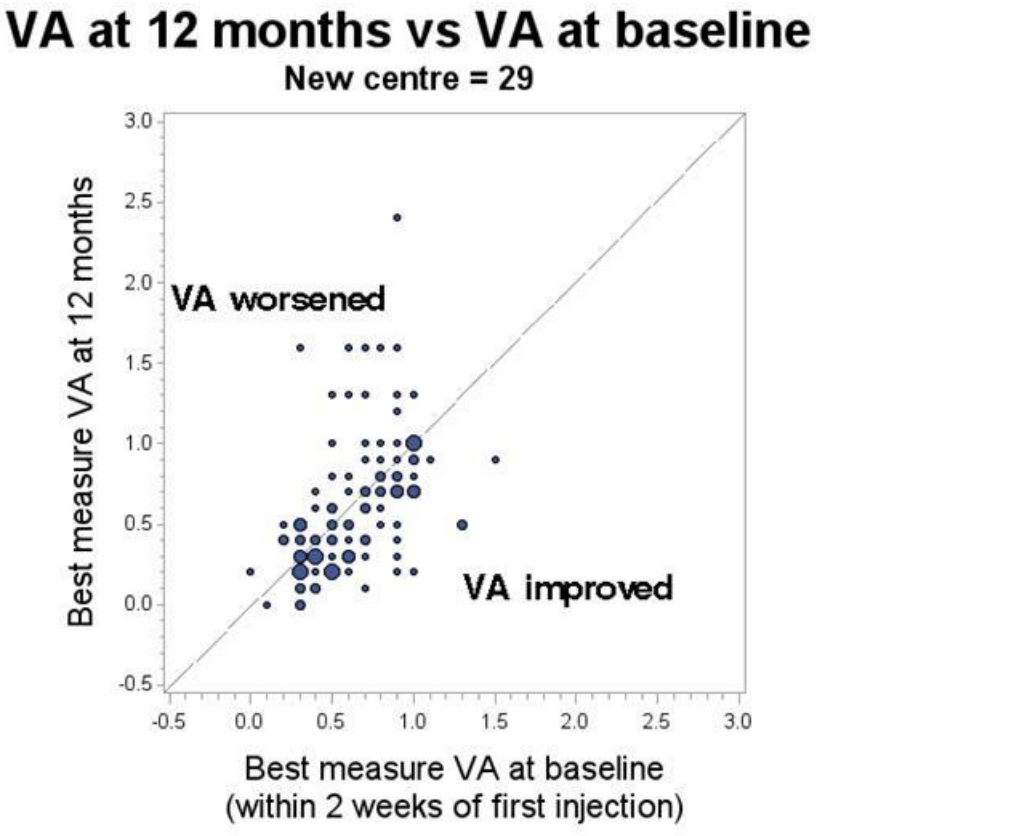

VA at 12 months vs VA at baseline
New centre = 24
Best measure VA at 12 months
VA worsened
VA improved
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

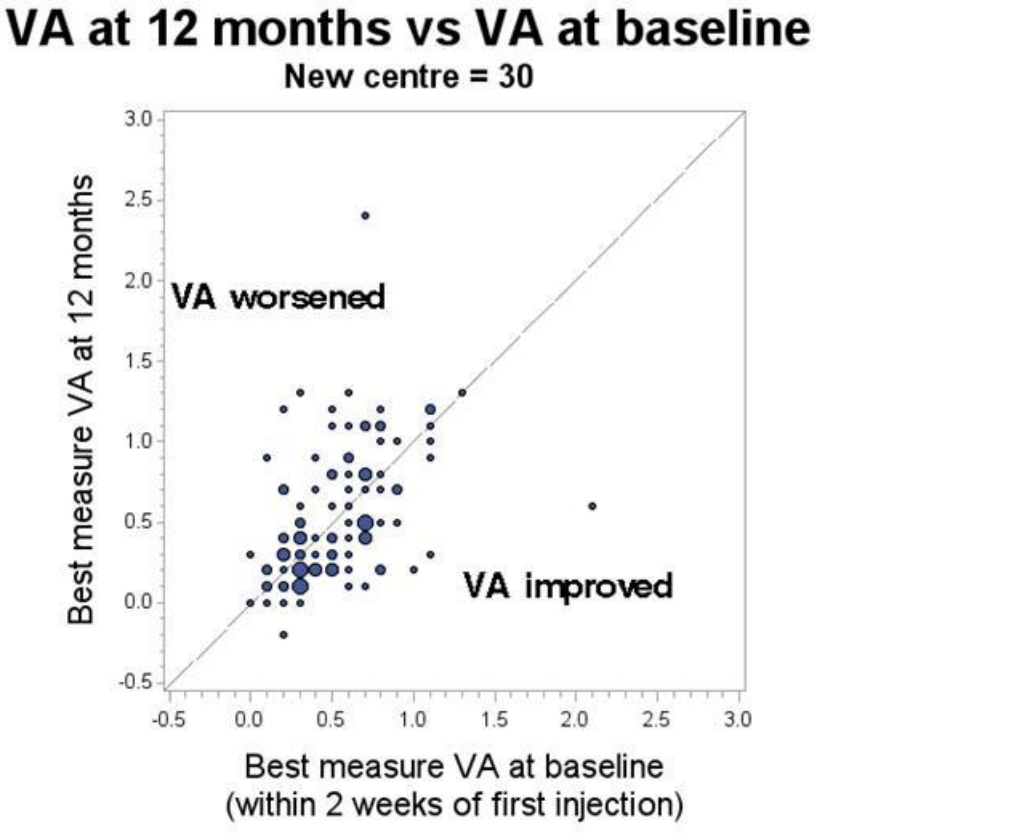

VA at 12 months vs VA at baseline
New centre = 25
Best measure VA at 12 months
VA worsened
VA improved
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

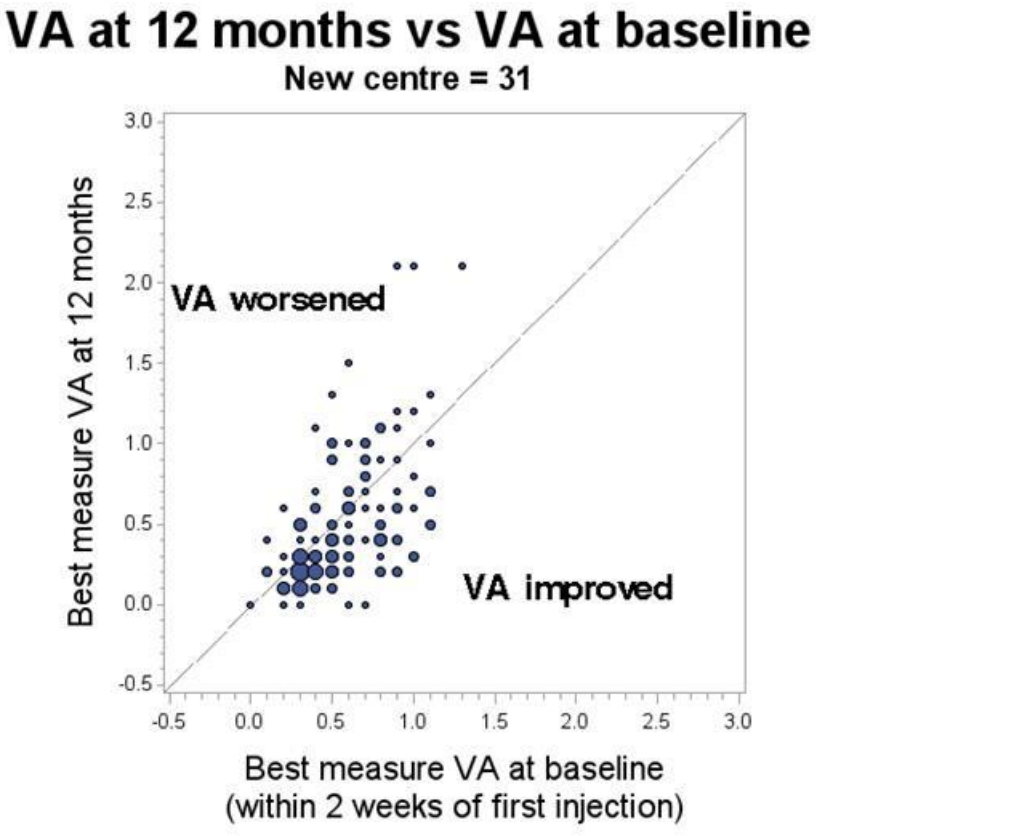

VA at 12 months vs VA at baseline
New centre = 26
Best measure VA at 12 months
VA worsened
VA improved
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point

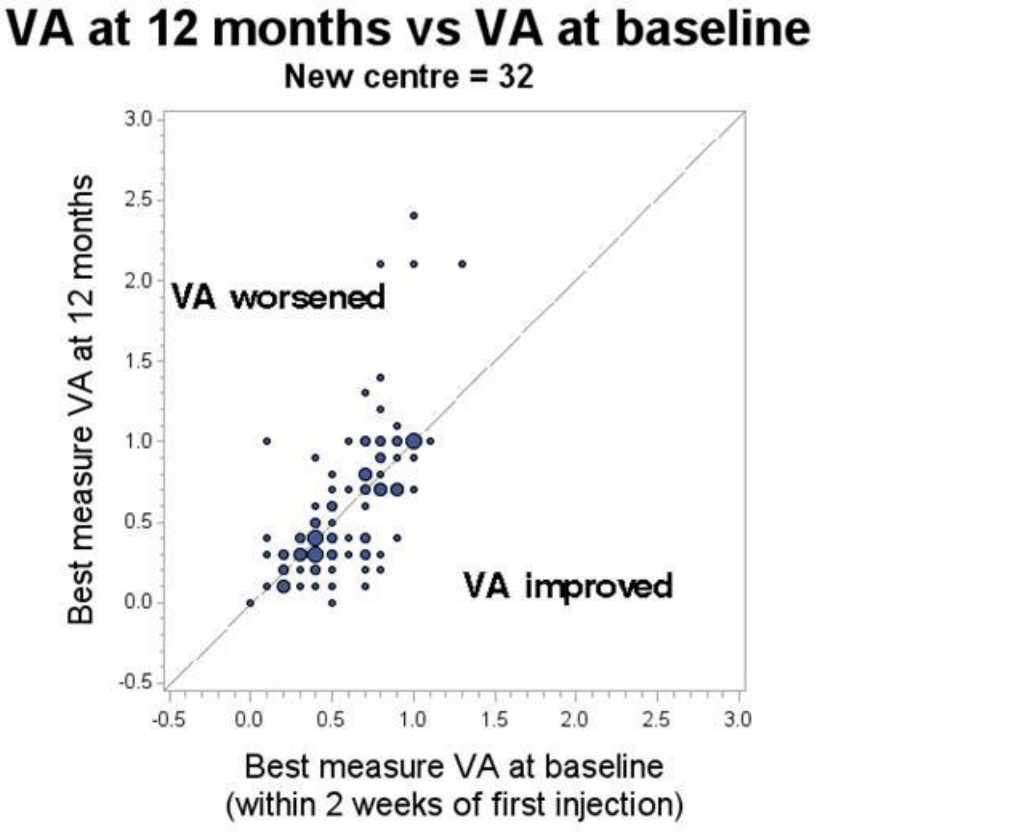

VA at 12 months vs VA at baseline
New centre = 27
Best measure VA at 12 months
VA worsened
VA improved
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point


VA at 12 months vs VA at baseline
New centre = 28
Best measure VA at 12 months
VA worsened
VA improved
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point


VA at 12 months vs VA at baseline
New centre = 29
Best measure VA at 12 months
VA worsened
VA improved
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point


VA at 12 months vs VA at baseline
New centre = 30
Best measure VA at 12 months
VA worsened
VA improved
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point


VA at 12 months vs VA at baseline
New centre = 31
Best measure VA at 12 months
VA worsened
VA improved
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point


VA at 12 months vs VA at baseline
New centre = 32
Best measure VA at 12 months
VA worsened
VA improved
Best measure VA at baseline
(within 2 weeks of first injection)
size of bubble proportional to
proportion (%) of observations at the point