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ASSESSING THE ACCURACY OF A LARGE OBSERVATIONAL REGISTRY OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

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Purpose: To evaluate the accuracy of an observational database that tracks real-world treatment outcomes for neovascular age-related macular degeneration.

Methods: We audited 245 randomly sampled eyes from 189 patients with 3,356 visits from 11 doctors in the Fight Retinal Blindness! database. Sex, birth year, previous treatments received, treatment, and visual acuity were validated against the clinical notes. Error rates, the proportion of missed visits (the number of visits present in the patient record but not entered into Fight Retinal Blindness!), the level of agreement using Cohen's kappa (κ) and intraclass correlation coefficients, and positive and negative predictive values were calculated. A visual acuity error was defined as an absolute difference of $\geq$5 letters.

Results: The overall error rate was 3.5% (95% confidence interval: 3.1–3.9). The error rate for visual acuity was 5.1% (95% confidence interval: 4.2–5.9) and $<$5% for the remaining fields. The level of agreement for each field ranged from good to excellent (κ or intraclass correlation $\geq$ 0.75). The positive predictive value and negative predictive value for visits were 99% and 89%, respectively. The proportion of missed visits was 10.2%.

Conclusion: Accuracy of the Fight Retinal Blindness! database was good ($>$95%). The rate of missed visits was high, possibly due to the high burden of retrospective data entry or patients switching practitioners during treatment.

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Population-based health care databases for monitoring patient outcomes in ophthalmology are becoming more prevalent.[1–5] Such registries can provide valuable data for epidemiological research and health care providers to improve quality of care.[6] However, the utility of these registries may be limited by the quality of the data they contain, and they are rarely validated.[7] Data quality reviews of registries in other medical fields have found that these databases are susceptible to inaccurate or missing data input.[8,9]

The Fight Retinal Blindness! (FRB!) project, a large postmarketing observational registry for neovascular age-related macular degeneration (nAMD), monitors treatment outcomes in nAMD to provide ongoing information regarding the efficacy, safety, and patient preference and quality of life of treatments after their regulatory approval. To validate the use of health care databases as a tool for tracking real-world outcomes in ophthalmic practice, we evaluated the accuracy of the FRB! database by performing a retrospective audit that compared data recorded in the database with the doctors' own clinical records.

Methods

Fight Retinal Blindness! Registry

Details of the FRB! observational registry have been described previously.[10] The database tracks real-world treatment outcomes in patients with nAMD during routine clinical practice and is compliant with the International Consortium for Health Outcomes Measurement's age-related macular degeneration minimum outcomes set.[11] Data are entered through a web-based interface in which the treating practitioner records standardized information at each visit. A summary of

the fields recorded in the database at baseline and subsequent follow-up visits, and which fields were included or excluded from the audit, is shown in Table 1. Practitioners participating in the registry are required to enter data for at least 85% of patients beginning treatment for nAMD in their practice to satisfy the self-audit component that is required for ongoing medical registration in Australia.

Institutional ethics approval was obtained from the Human Research Ethics Committees of the Royal Victorian Eye and Ear Hospital, the Royal Australian and New Zealand College of Ophthalmologists, and the University of Sydney. Ethics committees in Australia and New Zealand approved the use of opt-out patient consent. The FRB! project adhered to the tenets of the Declaration of Helsinki.

Data Validation Procedure

Participation in the FRB! audit was voluntary. Approximately 60 doctors in Australia and New Zealand were contacted before conducting the audit requesting permission for an independent reviewer to access their patient records. We received responses from 18 doctors agreeing to participate in the audit. Not all of these doctors were audited either because of logistical constraints of sending an independent reviewer to their practice or insufficient data to justify inclusion into the audit. The final audit included 11 doctors each with a minimum of 20 patients in the audit who collectively contributed data for 2,344 eyes of 1,891 patients, representing a third of the eyes entered into the FRB! database at the time the audit was initiated. It was estimated that a random sample of approximately 10% of patients from each doctor would be sufficient to give a confidence interval width of 5% assuming an error rate of 5% in the baseline fields. Data on both eyes were audited in patients receiving treatment to both eyes because clinical notes would generally keep information on both eyes together in such cases, although baseline demographics such as birth year and sex were only checked once per patient. All follow-up visits from sampled patients were audited regardless of follow-up duration.

Statistical Analysis

An error was defined as a discrepancy between the clinical records and the data as entered in the FRB! database. An error in visual acuity was defined as an absolute difference between the clinical record and the FRB! database of $\geq$5 letters (1 line of vision). The overall, field-specific and doctor-specific error rates were estimated as the frequency of cases in which an error was recorded divided by the total number of entries that were checked. Cases that could not be validated because of the unavailable source record from the practice were excluded from the error calculation. Confidence intervals for error rates were estimated assuming a binomial distribution. We also calculated the size and distribution of all discrepancies in visual acuity, including those that were $\geq$5 letters.

We measured the level of agreement between the clinical and FRB! records using Cohen's kappa statistic (κ) for categorical variables (sex, year of birth, pretreatments, and treatments) and the intraclass correlation for continuous variables (visual acuity). We interpreted κ and intraclass correlation based on previously suggested guidelines, with values $<$0.9 indicating excellent agreement, values between 0.75 and 0.9 indicating good agreement, values between 0.5 and 0.75 indicating moderate agreement, and values below 0.5 indicating poor agreement.[12,13] The positive predictive value (PPV) and negative predictive value (NPV) were calculated for treatments administered and patient visits.

The frequency and proportion of missed visits was also recorded. A missed visit was defined as a visit present in the patient record that has not been entered in the FRB! database. The proportion of missed visits was calculated as the number of missed visits divided by the total number of follow-up visits, both missed and recorded. Baseline visits were excluded from this calculation because, by definition, they could not be missing and visits were only counted once per patient.

Analyses were conducted in R V.3.4.4 using the *psych* package (V.1.8.4) to calculate κ and intraclass correlation statistics.[14,15]

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Table 1. List of Fields Recorded in the FRB! Database and Rationale for Excluding Fields That Were Not Validated

Field	Description	Visit Type	Rationale for Exclusion
Sex	Sex of the patient	Baseline only	Audited
Year of birth	Birth year of the patient	Baseline only	Audited
Previous treatment	Pretreatment status of the patient	Baseline only	Audited
Treatment	Treatment that was administered for that visit	Baseline and follow-up	Audited
Visual acuity	Number of letters read on a logMAR scale. Best of uncorrected, corrected, and pinhole	Baseline and follow-up	Audited
Ethnicity	Ethnicity of the patient	Baseline only	Subjective, may not be recorded in clinical notes
Angiographic lesion type	Lesion classification using fluorescein angiography and/or optical coherence tomography, judged by the treating clinician	Baseline only	Requires assessment of images and beyond expertise of independent assessor
Lesion size	Greatest linear dimension of lesion	Baseline only	Requires assessment of images and beyond expertise of independent assessor
CNV activity	Lesion activity status as graded by the treating clinician as active if there was subretinal or intraretinal fluid or new hemorrhage that suggested lesion was active.	Baseline and follow-up	Requires assessment of images, highly subjective and beyond the expertise of independent assessor
Geographic atrophy	Presence/absence and location of geographic atrophy	Baseline and follow-up	Field introduced in 2016 to comply with ICHOM so unavailable for most of the data. Requires assessment of images and beyond the expertise of independent assessor.
Subretinal fibrosis	Presence/absence and location of subretinal fibrosis	Baseline and follow-up	See *Geographic Atrophy*
Retinal pigment epithelial detachment	Presence/absence, type, and location of pigment epithelial detachment	Baseline and follow-up	See *Geographic Atrophy*
Adverse events	Treatment complications	Follow-up only	Extremely rare and unlikely to be captured in substantial numbers in a random sample of data. Estimates of error likely to be inadequate.
Discontinue reason	Reason for discontinuation of the patient from FRB! database. This field is optional and recorded only on the visit of discontinuation.	Follow-up only	Rare and unlikely to be captured in substantial numbers in a random sample of data. Entry is only required on visit of discontinuation, so it will not be applicable in a majority of cases.

CNV, choroidal neovascularization; ICHOM, International Consortium for Health Outcomes Measures.

Results

Observations on a total of 245 eyes of 189 patients made during 3,356 visits were audited from the FRB! database. There were 178 visits and 10 patients from the random sample that could not be audited because the source record was unavailable (e.g., practice records were missing, or patient records were offsite at the time the reviewer attended the practice).

A summary of the overall and field-specific error rates is shown in Table 2. The overall error rate was estimated to be 3.5% (95% confidence interval: 3.1–3.9) for the fields that were audited. The field with the highest error was visual acuity, with an error rate

Table 2. Overall and Field-specific Error Rates, and the Level of Agreement Given by Cohen's Kappa or the Intraclass Correlation Coefficient

Field	Frequency of Errors	Rate of Errors, % (95% CI)	Level of Agreement (95% CI)*
Sex	3	1.6 (0.4–5.0)	0.97 (0.93–1.00)
Year of birth	5	2.7 (1.0–6.4)	0.95 (0.97–1.00)
Pretreatment	7	3.7 (1.6–7.8)	0.86 (0.76–0.96)
Treatment	67	2.0 (1.6–2.6)	0.96 (0.97–0.98)
Visual acuity	168	5.1 (4.3–5.9)	0.98 (0.98–0.98)
Overall	251	3.5 (3.1–3.9)	—

*Cohen's Kappa (κ) for sex, year of birth, pretreatment and treatment, and intraclass correlation for visual acuity.
CI, confidence interval.

of 5.1% (95% confidence interval: 4.3–5.9) (Figure 1). Error rates for the remaining fields were under 5%.

The overall rate of missed visits was 10.2%. The positive predictive value for visits was 0.991, indicating that if a visit was present in the FRB!, then there was a 99% chance it actually occurred. The NPV for visits was 0.894, indicating an 89% chance that there is no missed visit between any 2 visits recorded in the FRB!

Discrepancies in visual acuity between the FRB! and clinical records were predominantly due to errors in conversion from Snellen to logMAR (n = 86) or not using the best of corrected, uncorrected, or pinhole visual acuity (n = 58), which collectively contributed to approximately 85% of all errors in visual acuity ≥5 letters. The remaining errors were possibly typographical, but otherwise the cause could not be inferred based on the records. When considering all discrepancies in visual acuity, including those within the acceptable margin of error (<5 letter difference), the median (Q1, Q3) difference between the FRB! and clinical records was −1 letter (−5, 2). Visual acuity was lower in the FRB! records than in the clinical records in 60% of the cases, indicating that the FRB! values were likely to be slight underestimates. The largest difference between the FRB! and clinical record was 76 letters. The overall distribution of all errors in visual acuity is shown in Figure 1.

Of the 67 errors (2.0% error rate) in the treatment field, there were 23 (34%) cases in which the FRB! database recorded no treatment administered for that visit despite a treatment recorded in the doctor's records. Conversely, there were 28 (42%) cases in which a treatment was recorded in the FRB! database despite no treatment administered in the doctor's records. The remaining 16 (24%) cases were the result of the incorrect treatment being recorded, for example,

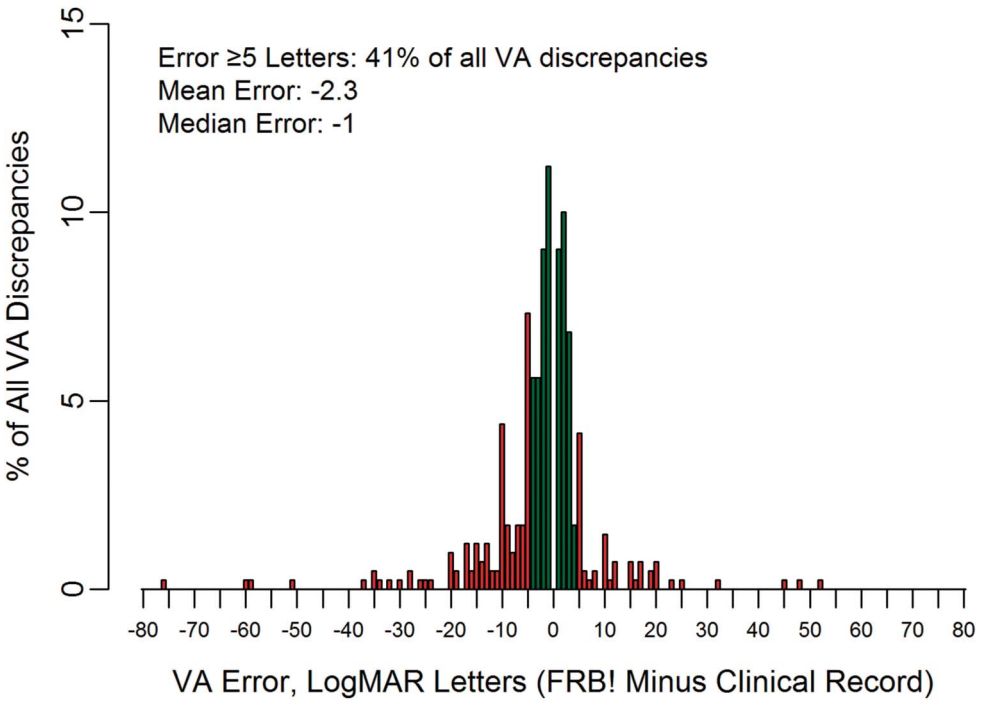

Fig. 1. Histogram showing the distribution of errors in visual acuity (VA), calculated as the FRB! record minus the clinical record, as a percentage of all VA discrepancies. Green bars indicate the discrepancy that was within the acceptable range of <5 letters, whereas red bars indicate errors that were ≥5 letters. The FRB! records had lower visual acuity compared with clinical records in 60% of the errors, indicating the FRB! records are slightly underestimating vision.

ranibizumab instead of aflibercept. The positive predictive value for any treatment being administered was 0.989, indicating that if any treatment was recorded in the FRB! database, then there is a 98.9% chance that a treatment was truly administered on that visit. Conversely, the NPV for any treatment being administered was 0.968, indicating that if no treatment was recorded in the FRB! database, then there is a 96.8% chance that no treatment was administered. For individual drugs, the positive predictive value and NPV was 0.954 and 0.996 for bevacizumab, 0.987 and 0.993 for ranibizumab, and 0.992 and 0.995 for aflibercept, respectively.

Overall doctor-specific error rates ranged from 1.5% to 9.9% (mean: 3.8% and median: 2.5%) when considering only clinically significant errors for visual acuity. Doctor-specific rates of missed visits ranged from 0% to 25.3% (mean: 5.6% and median: 5.2%).

Discussion

Observational studies have the advantage of high external validity because they obtain data from routine clinical practice. The FRB! project has investigated numerous aspects of the management of nAMD since its introduction, including outcomes of patients with bilateral disease, persistently active lesions, different treatment regimens, long-term treatment, adverse events (such as endophthalmitis and retinal pigment epithelial tears), cataract surgery, and comparison of outcomes with Phase 3 clinical trial data.[16–24]

The present audit supports the validity of findings from these previous analyses of FRB! data. We found that there was a low overall error rate (3.5%) and good or excellent agreement for the fields that were analyzed (Table 2). Of these fields, visual acuity had the highest frequency of errors, with 5.1% of entries having a $\geq$5 letter difference between the source and FRB! records (Figure 1). Our rates are similar to previously published audits on health registries such as the National Cardiovascular Data Registry (83.7%–95.7% accuracy), the National Program of Cancer Registries (95% accuracy), and the American Heart Association National Stroke Registry (>90% accuracy for all but 3 variables measured).[25–27] When considering all discrepancies between visual acuity recorded in the FRB! and clinical records, the median difference was -1 letter, indicating a slight tendency to underestimate visual acuity in the FRB! records but otherwise close to the source data measurements.

Incorrect conversion of visual acuity from Snellen to logMAR scales and not using the best recorded visual acuity (corrected, uncorrected, or pinhole) were the main causes of errors in visual acuity data exceeding 5 letters. We have since incorporated an automated conversion from Snellen to logMAR visual acuity scores into the FRB! website to reduce the frequency of these errors, particularly for users who are not familiar with logMAR visual acuity. There were also some difficulties in auditing the data because of poor legibility of information in handwritten clinical records or different visual acuity measurements recorded by the practitioner and their assistant at some visits. Transitioning to an electronic health record would eliminate mistakes in data translation due to illegible handwriting.

There was a high rate of missed visits (10.2%) with an NPV of 89%. Missed visits mostly occurred when the baseline visit was recorded, but the first few years of treatment were omitted. These were likely patients whose baseline visit had been entered retrospectively when the treatment had started several years earlier and follow-up visits were then entered prospectively. The high burden of retrospective data entry for these patients is the most likely reason for this result. In addition, patients who moved between providers may also have had large gaps in their visit history, which would contribute to the high rate of missed visits. Timely or simultaneous data entry into the FRB! database at the time of patient assessment, ideally by the clinician that assesses the patient, can reduce the rate of errors and missed visits,[28] although the appeal of tracking long-term outcomes for patients whose data are entered retrospectively should not be ignored. The FRB! database introduced a "treatment-only" visit option for users in 2017, which substantially reduces the number of mandatory fields that need to be entered. This would ease the burden of bulk data entry for patients with historical data to be entered, albeit at the cost of secondary information such as lesion activity. However, a visit with reduced information is preferred to no data at all. A long-term solution toward reducing data entry would be to introduce a single-point data entry system whereby the relevant data from the doctor's electronic medical records are automatically uploaded to the outcomes registry. However, such integration is difficult because of the unstructured nature of electronic medical records and incompatibilities between different providers.

The presence of missed visits could affect published results in a number of ways. Patients may be excluded from analyses, for example, if they are missing key milestone visits (e.g., 12 months) or if they do not meet the minimum treatment requirements for inclusion. Patients with large gaps in their visit history would have likely been removed from previously published FRB! analyses (e.g., Gillies et al[29]); thus, outcomes are unlikely to have been affected although

sample sizes would have been reduced. If patients with missing visits are still included after applying the selection criteria, the number of treatments would be underestimated and intervals between treatments overestimated. Previously published analyses of FRB! data have reported fewer treatments compared with clinical trials, but more than that reported in other real-world studies.[20,30] The loss of intermediate visual acuity measurements could also reduce resolution when estimating longitudinal trends over time. Defining strict selection criteria should reduce the impact of missed visits on published FRB! results, although ideally such data would be present and included in future analyses.

The errors between practitioners varied between 1.5% and 9.9%; the rate of missed visits was even more variable, ranging from 0% to 25.3%. Although the aims and interests of clinicians, patients, and research institutes are likely to differ, the FRB! system is designed to be robust and flexible to provide value to a diverse set of users while minimizing disruption to the users. The highly variable rate of errors is therefore a reflection of the differing interests, value propositions, and workflows between practitioners. For example, practitioners wishing to communicate the benefits of treatment to patients can display the visual acuity history for their patients, in which case the visual acuity at baseline is necessary for context but not necessarily all of the intermediate visits. Other users may enter the data periodically in bulk rather than at the time of patient assessment due to time constraints, which could increase the chance of errors and missed visits.

Limitations of this study include the restriction of fields that were audited, potential bias in the selection of practitioners who volunteered to be audited, and the possibility that the practice records also contained errors, the last issue further complicated by missing or illegible clinical notes. Our study is therefore only an approximation of the quality of data found in the FRB! database. Error rates may be higher in fields that were not included in this audit, such as whether a choroidal neovascularization lesion was active or not. Adverse events and reasons for discontinuation were not included in our study because of the infrequency of these events, and it is possible that they are underreported in the FRB! database. Fields designed to capture data that require the interpretation of images such as lesion activity, subretinal fibrosis, or geographic atrophy are vulnerable to observational bias and may require an independent reading center audit to adjudicate their grading. Recent advances in machine learning for image analysis could be a solution to reduce subjectivity and possibly reduce errors in fields requiring image assessment, if they are found to be unacceptably high.[31,32] However, there is a distinction to be made between errors in data entry, which was the focus of this audit, and misdiagnoses by clinicians, which is a much larger issue and beyond the scope of this study. Selection bias may also be present because participation in this data quality review was entirely voluntary. This self-selected group of practitioners from the FRB! database may have lower error rates or better compliance than the remaining practitioners who did not respond or refused to participate in the review. Indeed, these doctors collectively contributed to approximately a third of the overall data, suggesting that they are highly active within the registry.

This audit has demonstrated that there is a high accuracy rate of data recorded in the FRB! registry. Automated conversion of visual acuity from Snellen and logMAR should further reduce errors, particularly for users unfamiliar with logMAR. The rate of missed visits was high and likely due to the high burden of retrospective data entry. Treatment-only visits with fewer mandatory fields were introduced to reduce this burden. Single-point data entry is an ideal long-term solution toward reducing the burden of data entry; however, implementing such a system poses several challenges. Ongoing audits of observational registries are necessary to ensure maintenance of an adequate quality of data that is appropriate for analysis.

Key words: observational data, registry, data quality, audit.

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