Statistical Analysis Plan for a randomised controlled trial: An educational intervention to improve Attitudes and overcome Barriers to Care in Age-related Macular Degeneration.

Gordon S. Doig[1] and Angelica Ly[2]
on behalf of the Trial Management Committee.

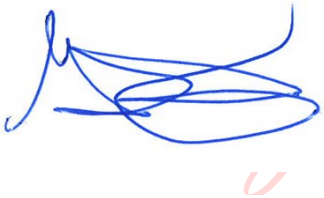
The ABCs of AMD RCT

Australian and New Zealand Clinical Trials Registry Number ACTRN12622000984796

[1] Sydney Medical School, Faculty of Medicine and Health, University of Sydney, Sydney. [2] School of Optometry and Vision Science, Faculty of Medicine and Health, University of New South Wales, Sydney.

Corresponding author:
Dr. Gordon S. Doig,
Sydney Medical School,
Faculty of Medicine and Health,
University of Sydney, Sydney,
Australia 2006
Gordon.Doig@sydney.edu.au
www.EvidenceBased.net/files/ABCAMD_SAP.pdf

Title: **Statistical Analysis Plan for a randomised controlled trial: An educational intervention to improve Attitudes and overcome Barriers to Care in Age-related Macular Degeneration.**
Edition: Ver 1, Rev 1
Author/Contributor: Doig, Gordon S; Ly, Angelica.
Date of Publication: 28 June 2022
Format: WEB
Size: 297x210
No. of Pages: 13
Publisher: EvidenceBased.net, Sydney, NSW, Australia



Digitally signed by Dr Gordon Doig
DN: cn=Dr Gordon Doig, o=University of Sydney, ou=NCS ICRU, email=gdoig@med.usyd.edu.au, c=AU
Date: 2022.07.14 09:49:51 +10'00'

Contents

BRIEF BACKGROUND

1.1 Overview:

Guided by the principles of health literacy, an enhanced educational program was developed to influence attitudes towards appropriate care and thus help overcome barriers towards care seeking behaviours. We initiated and conducted a randomised clinical trial recruiting patients with intermediate or advanced AMD to be randomised to receive this enhanced educational program or pragmatic standard care.

1.2 Hypotheses to be tested:

In patients with intermediate or advanced AMD, the provision of an enhanced educational program alters attitudes towards appropriate care for AMD, compared to pragmatic standard care.

1.3 Eligibility criteria:

See **Appendix 1** for the complete list of study eligibility criteria.

1.4 Randomisation:

Allocation concealment was maintained through the use of sequentially numbered opaque sealed envelopes.[1]

The randomisation sequence was generated using blocks of variable size and random seeds [2] to ensure allocation concealment could not be violated by guessing the allocation sequence at the end of each block. Randomisation was stratified within study site with block sizes concealed from site investigators to further prevent anticipation of the allocation sequence.[1]

1.5 Study intervention:

If allocated to *Enhanced education*, the participant's usual care process will remain unchanged and education will be provided by the attending clinician ***plus*** the participant will be provided with resources to access at home that explain what this diagnosis means and presents a number of treatment options / monitoring activities using an optimally engaging format with easily understood language.

The *Enhanced education* package will include decision support tools, evidence summary documents which provide easy access to web pages containing additional educational presentations, options to sign up for telephone / SMS or web based reminders and other elements identified in our Pilot project to be important for overcoming specific barriers to change.

1.6 Pragmatic Standard Care:

If allocated to pragmatic *standard care*, the participant's usual care process will remain unchanged and education will be provided by the attending clinician as per their usual care processes.

1.7 Data collection and follow up:

Every appropriately enrolled and randomised patient will be followed up 6-months post-randomisation, unless consent is withdrawn.

1.8 Study primary outcome:

The study primary outcome will be a composite measure of *confidence in the benefits of appropriate care for AMD,* compared between groups at 6 months after study enrolment.

This composite outcome will be composed of the sum of individual measures of *confidence in the benefits of*: using an Amsler Grid; quitting smoking; taking eye health supplements and receiving eye injections. Confidence in the benefits of each form of care will be measured at study baseline and at 6 month follow-up using a balanced 5-point Likert scale.

1.9 Missing primary outcomes:

Although the individual components of the primary composite outcome are worded such that all participants should provide a response, it is possible that responses to some of these individual components will be missing.

Missing individual components of the composite primary outcome will be assumed to be missing at random (MAR) and thus will be 'ignored' in the primary analysis [3] unless greater than 5% of all individual components that should be available for analysis are missing, in which case the primary analysis will include imputed values.

If required, values will be imputed under the following assumptions:

Group Mean Imputed: For any missing individual component, the *group mean* for that specific individual component will be imputed and added to the sum score in place of the individual patient's missing component.

If imputation is required, results of the imputed analyses will take precedence over the primary MAR analysis, but will be interpreted in the context of the primary MAR analysis.

Information that is *unavailable* for analysis due to withdrawal of consent for data use will not be considered *missing* and therefore will not be included in the estimate of percent missing as described above nor will it be included in a simulation study.

STATISTICAL ANALYSIS

2.1 Interim analysis:

To address ethical considerations related to withholding interventions with convincing benefits or exposing patients to futile study interventions, one interim analysis will be conducted when 50% of the recruitment target achieves 6 month outcomes. This interim analysis will consider only the study primary outcome.

Using the Haybittle-Peto approach, [4,5] the trial may be stopped for convincing early benefit if the treatment effect in favour of the active study intervention (enhanced education) exceeds three standard deviations in magnitude (standardized z score of +3). Covariate adjustment for baseline and potential confounders will be considered when assessing this threshold. Interim analysis using Haybittle-Peto thresholds for convincing early benefit does not impact the final overall p-value for interpretation of statistical significance.

At this mid-point interim analysis, a pre-specified boundary for futility will be set at a conditional power of < 20% for finding a significant effect in favour of the active study group (enhanced education) at final analysis. This equates to a standardised z score of -1.24092 obtained using SAS Proc SeqDesign in favour of standard care.

2.2 Sample size and power:

130 participants will be recruited and followed-up for 6 months.

A Cohen's *d* (effect size) of 0.5 is accepted to represent a moderate (medium) sized treatment effect. [6] Previous publications suggest the expected SD for a 5-point Likert scale eliciting *attitudes toward appropriate treatments* is approximately 1.[7] Thus, a 126 participant clinical trial (63 participants in each

group) would provide 80% power to detect a moderate (medium) sized treatment difference between groups of a 0.5 change in attitudes.

Although routine clinical trials follow-up methods will be employed to minimise loss to follow-up at 6 months, the initial estimate of 126 participants will be increased to 130 participants to protect against loss of power due to unavoidable drop-outs (withdrawal of consent, moving out of state, deaths etc).

2.3 Basic principles of analysis:

The primary conclusions of this project will be based on analyses conducted under the principle of intention to treat: All randomised patients will be analysed in the groups to which they were originally allocated to, regardless of whether a subsequent protocol violation or protocol deviation occurred.

It is accepted that an overly rigid application of the principle of intention to treat may increase the chance of a Type II error in an analysis of *efficacy* (as opposed to effectiveness). [8;9] To minimise Type II errors in an analysis of *efficacy*, authoritative sources have proposed that minor *modifications* to an intention to treat analysis are appropriate. Bias may be avoided and random error may be minimised by exclusion of the following patient groups from the primary *modified* intention to treat analysis: **1)** Patients who were *mistakenly enrolled* and stand no chance of benefit; and **2)** Patients who were *prematurely randomised* resulting in failure to deliver the allocated intervention. [9]

The primary *modified* intention to treat analysis for *efficacy* will therefore exclude patients who were enrolled by *obvious mistake* who stand no chance of benefit (Ex. Patient does not actually have AMD) and will exclude patients who were *randomised prematurely* (Ex. Randomised before they actually attended their first study baseline visit and then they fail to attend the baseline visit).

The decision to exclude patients from the modified intention to treat analysis of *efficacy* based on *mistaken enrolment* and *premature randomisation* will be made by an adjudication committee blinded to study group and patient outcome.

An (unmodified) intention to treat analysis will be conducted, with results reported to support inferences regarding *effectiveness*.

Patients who withdrew consent for use of their data will not be included in any analysis. Only the facts that they were enrolled into the trial and withdrew consent, and the original study group to which they were allocated, will be reported.

A two-sided 5% significance level will be used to identify statistically significant results. A two-sided 10% significance level will be used to identify results that are trending towards statistical significance. All confidence intervals reported will be 95% confidence intervals.

Adjustments for multiplicity will not be undertaken because a hierarchy of outcomes has been stipulated [10] and because the conduct of an interim analysis using Haybittle-Peto stopping thresholds does not require adjustment of outcomes for multiplicity. [4,5]

2.4 Initial analysis of primary outcome:

Linear regression will be used to assess between groups differences in the primary outcome collected at 6 months after enrolment.[11] Baseline values of the composite measure of *confidence in benefits of care* will be included in this *initial* analysis as a covariate. [12]

The magnitude of the treatment effect will be reported as an absolute difference between groups, with 95% confidence intervals.

2.5 Distribution of baseline prognostic variables (aka Manuscript Table 1):

Baseline prognostic variables, ascertained at time of study enrolment, will be reported by study group in Manuscript Table 1.

Continuous variables, which are expected to be Normally distributed under the Central Limit Theorum, will be presented as Mean and Standard Deviation. Dichotomous variables will be presented as Numerator/Denominator and Percent.

2.6 Missing baseline prognostic variables:

Exclusion of randomised patients with known outcomes from analysis may contravene the intention to treat principle. [13] Every effort should be made to minimise post-randomisation exclusions. [3]

By default, statistical software packages require complete information on all covariates for a patient case to be included in a covariate adjusted regression model. Any missing information from any covariate results in the exclusion of the entire patient case by the software package. Exclusion of incomplete cases with known outcomes reduces statistical efficiency and introduces bias into the estimate of treatment effect. [14,15,16]

Missing baseline prognostic variables will be replaced with mean values calculated from the observed non-missing instances of that baseline prognostic variable. [17] The imputed values will be calculated using pooled data from **both** treatment arms. Imputed means will *not* be calculated within treatment arm using treatment arm-specific data *nor* will any post-randomisation information be incorporated into the calculation. Furthermore, replacement values for missing calculated constructs such as *confidence in benefits of treatment* score will be estimated using non-missing component-level information. For example, if one of the components is missing, such as *confidence in the benefits of quitting smoking*, overall mean *confidence in the benefits of quitting smoking* will be imputed and composite score will be calculated with the other known variables and imputed mean *confidence in the benefits of quitting smoking*.

If a baseline prognostic variable requires imputation of missing values, the percent of cases that were originally missing will be reported.

2.7 Covariate adjusted analysis of primary outcome:

A *covariate adjusted analysis* of the effect of treatment on the primary outcome will be undertaken. An objective pre-specified algorithm will be used to select variables for inclusion in the covariate adjusted regression model. [18] The primary purpose of the covariate adjusted analysis will be to remove bias from the estimate of the treatment effect on the primary outcome.

All prognostic variables reported in Manuscript Table 1 (see Section 2.7) will be eligible for inclusion in the covariate adjusted analysis. *Interaction terms* will not be considered in the covariate adjusted model. [18]

Step 1: *Identification of prognostic variables with a strong association with outcome*

Prognostic variables shown to be strongly associated with outcome, even if not shown to be imbalanced between treatment groups, will be screened for inclusion in the covariate adjusted model as they may remove bias from the estimate of treatment effect. [18,19,20,21]

Univariate linear regression analysis will be conducted to evaluate the relationship between each prognostic variable identified in Section 2.5 *and the study primary outcome*.

Prognostic variables with a univariate p-value less than or equal to 0.15 will qualify for evaluation in the *maximum covariate adjusted model* (see Step 3). [22] Inferences will not be drawn from the interpretation of this univariate p-value, the p-value will simply be used to describe the *strength* of association between the prognostic variable and the primary outcome. [20]

Step 2: *Identification of prognostic variables with strong imbalance between treatment groups*
Prognostic variables shown to be strongly imbalanced between treatment groups, even if associations with outcome are shown to be weak, will be screened for inclusion in the covariate adjusted model as they may remove bias from the estimate of treatment effect. [18,19,20]

Univariate linear regression analysis will be conducted to evaluate the relationship between each prognostic variable identified in Section 2.5 *and allocated treatment group*.

Prognostic variables with a p-value less than or equal to 0.15 will qualify for evaluation in the *maximum covariate adjusted model* (see Step 3). [22] Inferences will not be drawn from the interpretation of this p-value, the p-value will simply be used to describe the *strength* of imbalance between treatment groups. [20]

We acknowledge that simulation studies demonstrate the addition of this step *may not* improve performance over 'predictor' detection alone (Step 1) however these simulations are not definitive. [21] 'Imbalance' detection *may* help preserve the face validity of the covariate adjusted results [23] and *may* remove bias from the estimate of treatment effect. [22,23]

Step 3: *Backwards stepwise elimination from the maximum model*
All prognostic variables identified by Step 1 and Step 2 will be included in a *maximum covariate adjusted linear regression model.* The treatment group term will be forced to stay in the maximum model. The model outcome will be the study primary outcome.

If the maximum model demonstrates issues arising due to collinearity based on Eigenanalysis and Condition Number, collinearity will be addressed by: **1)** if variables are found to be exact linear combinations of each other, collinearity will be reduced by eliminating the component of one variable contributing the least amount of information (Ex. Replace A with B); **2)** if required, continuous variables will be standardized and scaled and **3)** if required, one pair of a highly correlated set of variables may be eliminated, such that minimal information is lost. [24] Formal Backwards Stepwise elimination will begin only after collinearity has been adequately addressed.

Step 3a: Prognostic variables will be eliminated from the maximum model, one variable at each step, if their covariate adjusted p-value is greater than 0.10. Elimination will start with the variable with the largest p-value.

Step 4: *Final covariate adjusted model*
The *final* covariate adjusted model will contain all prognostic variables remaining in the model after completion of Step 3a. The complete *final* model will be presented as the *covariate adjusted model* in the primary paper.

The p-value for the estimate of treatment effect from this model will be reported.

If the results of the covariate adjusted analysis of the primary outcome differ in any meaningful way from the results of the initial analysis of the primary outcome with regards to statistical significance thresholds or estimation of the magnitude of treatment effect, the primary conclusions of the study will be based on the results of the covariate adjusted analysis.

2.8 Establishing Minimal Important Differences:

Within the context of the interpretation of health-related quality of life (HRQoL) measures, a Minimal Important Difference (MID) is defined as a magnitude of change in (or difference between) HRQoL scores that is "consistent with real, as opposed to statistically significant, benefit." [27] We will therefore define our thresholds for MIDs for our primary outcome, and other HRQoL measures, *a priori*.

In the situation where *statistically significant* results are reported *and* the magnitude of the differences between groups with regards to a HRQoL measures is *greater than or equal to* the MID, the results will be

interpreted as representing statistically significant findings that have a *clinically meaningful* impact on the patient's HRQoL.

If the results are found to be *statistically significant* and the magnitude of difference is *less than* the MID, the findings will be interpreted to be statistically significant only.

Because the *responsiveness* of an HRQoL measure varies between patient populations and disease states, it is accepted that for any particular HRQoL measure, the MID may also be unique to each patient population and disease state. [28] When the *responsiveness* of a specific HRQoL measure has not been formally studied in a particular patient population or disease state, it is recommended that a formal method should be used to establish the population-disease specific MID using data collected from that particular population or disease state. [28]

Responsiveness and MIDs for the HRQoL measures used in this trial have not been reported for the patient population to be enrolled. We will therefore use a formal analytic approach to establish MID thresholds for each HRQoL measure. [28]

Using the approach proposed by Juniper [6] and validated by Norman [27], we will define a MID as one half the Standard Deviation (SD) of the pooled results for that measure. [28] Furthermore, differences in the magnitude of 1 SD will be described as having a *moderate* impact on HRQoL and differences in excess of 1.5 SDs will be described as having a *large* effect on HRQoL. [6]

2.9 *A priori* defined subgroup analysis:

Four subgroup analyses are planned *a priori*:

1) Duration of disease, with threshold to define two groups set at median duration reported in Question 3.2 (above median vs. below median).

2) Stage of AMD (highest stage intermediate AMD in one or both eyes vs. least advanced AMD in one or both eye).

3) Self reported quality of eyesight, with threshold to define two groups set at median score for Question 3.4 (above median vs. below median).

4) Self reported composite HLI score, with threshold to define two groups set at median score for composite sum of responses to all subsection HLI items under Question 5.1 (above median vs below median).

Screening for differential subgroup treatment effects on the primary study outcome will be conducted using a formal test of interaction. The results of the above described screening tests of interaction will be reported in the primary publication.

The linear regression model will contain a main effect term denoting the specific subgroup of interest, a main effect term for treatment group and a subgroup × treatment interaction term. If the two-sided p-value for this test of the subgroup × treatment interaction term is less than 0.10, the presence of differential treatment effects within subgroups will be reported in the primary publication along with the p-value for the interaction term.

Detailed subgroup analysis will be undertaken *only* within subgroups identified to have differential treatment responses by the screening process described above. Detailed subgroup analysis will adhere to the same analytic principles and plan outlined for the overall study results. Detailed subgroup analysis will include reassessment of the baseline distribution of prognostic variables within the subgroup of interest,

development of a subgroup appropriate covariate adjusted model and reassessment of all study outcomes within the subgroup. The results of any detailed subgroup analysis will be reported in subsequent papers, to be submitted for publication soon after the submission of the primary publication.

The number of *a priori* subgroup analyses (4) will be reported in all publications. Due to the use of conservative tests of interaction to screen for the need to conduct detailed analysis within subgroups, no corrections to p-values will be undertaken for multiple-comparisons.

2.10 Exploratory, hypothesis generating subgroup analyses:

No hypothesis generating subgroup analyses will be undertaken for or reported in the primary publication.

If any hypothesis generating subgroup analyses are reported in subsequent publications, they will be clearly identified as hypothesis generating when reported.

The number of *a priori* subgroup analyses will be reported in all publications along with the total number of any *hypothesis generating* subgroup analyses previously undertaken.

Reference List

(1) Doig GS, Simpson F. Randomization and allocation concealment: a practical guide for researchers. *J Crit Care* 2005;20:187-191.

(2) Schulz KF, Grimes DA. Unequal group sizes in randomised trials: guarding against guessing. *Lancet* 2002;359:966-970.

(3) Lachin JL. Statistical considerations in the intent-to-treat principle. *Control Clin Trials* 2000;21:526.

(4) Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *British Journal of Radiology* 1971;44:793-797.

(5) Peto R, Pike MC, Armitage P et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *British Journal of Cancer* 1976;34:585-612.

(6) Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol* 1994;47:81-87.

(7) Heighes PT, Doig GS. Evidence summary resources may influence clinical decision making: A case-based scenario evaluation of an evidence summary tool. *J Crit Care* 2020;55:9-15.

(8) Sommer A, Zeger SL. On estimating efficacy from clinical trials. *Stat Med* 1991;10:45-52.

(9) Fergusson D, Aaron SD, Guyatt G, Hebert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ* 2002;325:652-654.

(10) Statistical principles for clinical trials: ICH Topic E 9. 1998. www.emea.eu.int, European Medicines Agency.

(11) Norman G. Likert scales, levels of measurement and the "laws" of statistics. *Adv Health Sci Educ Theory Pract* 2010;15:625-632.

(12) Vickers AJ. The use of percentage change from baseline as an outcome in a controlled trial is statistically inefficient: a simulation study. *BMC Med Res Methodol* 2001;1:6.

(13) Schulz KF, Grimes DA. Sample size slippages in randomised trials: Exclusions and the lost and wayward. *Lancet* 2002;359:781-785.

(14) Schemper M, Smith TL. Efficient evaluation of treatment effects in the presence of missing covariate values. *Statistics in Medicine* 1990;9:777-784.

(15) Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh J, Norton R. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. *Intensive Care Med* 2011;37:86-96.

(16) Analysis of Incomplete Data. In: Dmitrienko A, Molenberghs G, Chuang-Stein C, Offen W, eds. *Analysis of clinical trials using SAS: A practical guide*. Cary, NC: SAS Publishing; 2008;269-354.

(17) White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials. *Statistics in Medicine* 2005;24:993-1007.

(18) Pocock SJ, Assmann SE, Enos LE, Kastan LE. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: Current practice and problems. *Statistics in Medicine* 2002;21:2197-2930.

(19) Senn SJ. Covariate imbalance in randomized clinical trials. *Statistics in Medicine* 1989;8:467-475.

(20) Senn SJ. Testing for baseline balance in clinical trials. *Statistics in Medicine* 1994;13:1715-1726.

(21) Negassa A, Hanley JA. The effect of omitted covariates on confidence interval and study power in binary outcome analysis: A simulation study. *Contemporary Clinical Trials* 2007;28:242-248.

(22) Hernandez AV, Steyerberg EW, Habbema DF. Covariate adjustement in randomized controlled trials with dichotomous outcomes increases statistical power and reduces sample size requirements. *Journal of Clinical Epidemiology* 2004;57:454-460.

(23) Cooper DJ, Rosenfeld JV, Murray L et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med* 2011;364:1493-1502.

(24) Uchino S, Doig GS, Bellomo R et al. Diuretics and mortality in acute renal failure. *Crit Care Med* 2004;32:1669-1677.

(25) Greenland S. Cautions in the use of preliminary-test estimators. *Statistics in Medicine* 1989;8:669-673.

(26) Rothman KJ. Epidemiologic methods in clinical trials. *Cancer* 1977;39:1771-1775.

(27) Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: The remarkable universality of a half a standard deviation. *Medical Care* 2004;41:582-592.

(28) Revicki D, Hayes RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient reported outcomes. *Journal of Clinical Epidemiology* 2008;61:102-109.

(29) Zubrod C, Schneiderman MA, Frei E et al. Appraisal of methods for the study of chemotherapy of cancer in man: Comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide. *Journal of Chronic Disease* 1960;11:7-33.

(30) Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-483.

(31) Guilfoyle MR, Seeley HM, Corteen E et al. Assessing quality of life after traumatic brain injury: examination of the short form 36 health survey. *J Neurotrauma* 2010;27:2173-2181.

(32) Fielding S, MacLennan G, Cook JA, Ramsay CR. A review of RCTs in four medical journals to assess the use of imputation to overcome missing data in quality of life outcomes. *Trials* 2008;9:51.

Appendix 1: Detailed Study Inclusion and Exclusion Criteria

Inclusion Criteria

Patients will be considered ***eligible*** for the trial if ***all*** of the following *inclusion criteria* are met at the time of screening:
(Answer **YES** to all questions to be eligible)

1. Is the patient 18 years of age or older?

2. Has the patient been diagnosed with intermediate or advanced AMD in at least one eye at the Centre for Eye Health?

3. Is the patient able to communicate effectively in English?

4. Does the patient intend to live in New South Wales over the next year?

Exclusion Criteria

Patients will be considered *ineligible* for the trial if *any* of the following *exclusion criteria* are met at the time of screening:
(Answer NO to all questions to be eligible)

1. Does the patient have another co-morbid ocular disease (e.g. glaucoma) requiring treatment?

Blank page

End of document.