Review Article

The Correction of Myopia Evaluation Trial: Lessons from the Study Design

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Abstract

The Correction of Myopia Evaluation Trial (COMET), a multicentre clinical trial based in 4 schools of optometry in the United States, evaluated the effect of progressive addition lenses versus single vision lenses on myopia progression in an ethnically diverse group of 469 myopic children aged 6 to 11 years. Completion of the clinical trial phase of the study provides an opportunity to evaluate aspects of the study design that contribute to its success. This article describes aspects of the study design that were influential in ensuring the smooth conduct of COMET. These include a dedicated team of investigators, an organisational structure with strong leadership and an independent Co-ordinating Centre, regular communication among investigators, flexible and creative approaches to recruitment and retention, sensitivity to concerns for child safety and child participation, and methods for enhancing and monitoring data reliability. The experience with COMET has provided a number of valuable lessons for all aspects of the study design that should benefit the development and implementation of future clinical trials, particularly those done in similar populations of children. The use of a carefully designed protocol using standard methods by dedicated members of the study team is essential in ensuring achievement of the study aims.

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Introduction

"A properly planned and executed clinical trial is a powerful technique for assessing the effectiveness of an intervention".[1] While each new clinical trial involves unique issues relevant to a particular condition or disease, overarching common guidelines for all studies provide the framework for obtaining meaningful results. These guidelines include the need for careful thought and planning before initiating the study, beginning with a statement of clearly defined aims and the development of a protocol that includes standardised methods of data collection and plans for data analysis. For multicentre studies, having a specified organisational structure with an independent centre for data monitoring, management and analysis is also essential. Consideration must be given to methods of recruitment to ensure that the predetermined sample size goals are met. Of equal importance is the development of methods to be used for retention of study participants over time. The Consolidated Standards of Reporting Trials (CONSORT) statement provides guidelines for reporting of randomised controlled clinical trials;[2] if those guidelines are considered while designing a study, the key aspects of clinical trial design will be followed.

The Correction of Myopia Evaluation Trial (COMET) was designed and conducted according to standard clinical trial principles. This multicentre clinical trial, based in 4 schools of optometry in the United States (US), evaluated the effect of progressive addition lenses (PALs) versus single vision lenses on myopia progression in an ethnically diverse group of 469 children with juvenile onset myopia.[3,4] As the first National Eye Institute-funded multicentre clinical trial in the US to be based in schools of optometry and to focus on myopia progression, COMET investigators were aware of the importance of setting a high standard for excellence in its design and conduct. The trial was designed to follow all enrolled children for at least 3 years in their assigned lenses and its main results were recently reported.[5] All children were recruited within a 1-year period and the recruitment goal of 450 children was exceeded. Retention was outstanding, with all but 7 children available for 3 years of follow-up. The trial results indicated a statistically significant 3-year difference in myopia progression of 0.2 ± 0.08 D between the 2 groups. The treatment effect was observed primarily in the first year and remained similar and significant for the next 2 years.

Now that the clinical trial phase of the study has been

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completed, we have an opportunity to evaluate which aspects of the study were most valuable in contributing towards its success. This article will focus on those practical aspects of the study design that were influential in ensuring the smooth conduct of COMET.

Creation of a Committed, Interdisciplinary Study Team

The creation of the COMET study team involved identifying investigators from different disciplines who were willing to work together, recognising that a successful study required input and full collaboration from individuals with expertise in myopia research in humans and animals, the science and conduct of clinical trials, including epidemiology and biostatistics, and clinical optometry. Once the Study Chair and Co-ordinating Centre were established and the overall study design developed, it was necessary to select clinical centres and co-investigators who would be responsible for recruiting children within the designated 1-year period according to a standard protocol. Since the success of the study was dependent on the ability of the study investigators to recruit and retain eligible families, as well as to collect high quality, accurate data, the appropriate selection of individuals and institutions that would co-operate fully was crucial. We sought to identify enthusiastic investigators with expertise in myopia who were based in optometric academic centres of excellence, and were willing to be part of a study team, work hard and provide leadership within their centre. Each of the 4 schools of optometry selected was committed to COMET's success and agreed to provide dedicated space for the study visits and study personnel. The principal investigators of each centre, along with the team they assembled at their institution, have remained dedicated to the study from the outset. They have provided input into the study protocol throughout, conducted all study visits according to the study protocol, developed an outstanding rapport with the study families, participated in manuscript preparation and provided strong leadership to other members of their teams. The high level of data quality and retention of COMET families throughout almost 5 years of follow-up is attributed primarily to these individuals and their team. The involvement of this multidisciplinary team who respected and learned from each other's expertise led to a genuine camaraderie that was fundamental to the successful development, implementation and monitoring of the study protocol.

Value of Study Committees/Organisational Structure

One necessity of a multicentre study design is a defined organisational structure and study committees with clearly delineated responsibilities. The inclusion of such a structure in COMET (Fig. 1), led by a Study Chair and an independent Co-ordinating Centre, provided a vital infrastructure for study leadership, decision-making, communication and independent monitoring. The Data and Safety Monitoring Committee (DSMC), an essential study committee, was responsible for monitoring child safety concerns and overall study performance throughout the clinical trial phase of the study. It also provided a mechanism to ensure that child safety issues, as well as the possibility of early study termination, were considered. The Steering Committee comprised principal investigators of each study centre, and consultant to the Study Chair, additional Co-ordinating Centre personnel and representative of the National Eye Institute (NEI) reviewed data on protocol adherence, retention and data quality routinely to address protocol-related issues on an ongoing basis. Close monitoring of the study allowed for timely adjustments to be made to the protocol as needed. The role of the NEI representative was to serve as a liaison between the sponsor and the trial, as well as to provide administrative and fiscal advice. His involvement in the trial committees was important in facilitating communication between the COMET investigators and the NEI.

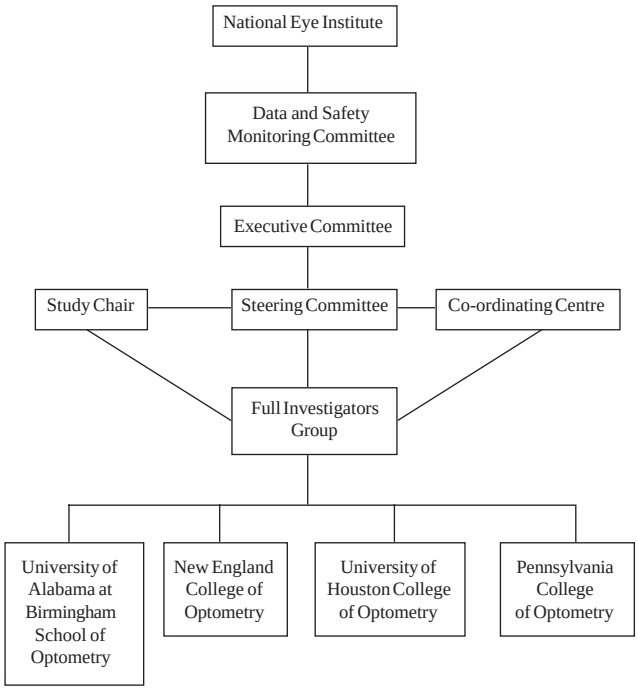

Fig. 1. Organisational structure.

Importance of Regular Communication Among Centres

Communication among study investigators included routine meetings and conference calls. Regular communication provided a vehicle for exchange of information and ideas and allowed for prompt resolution of new issues. Monthly Steering Committee and Clinic Co-ordinator conference calls were held and documented by distributing minutes to all study investigators shortly after the calls were completed. Annual meetings were held for the Full Investigator Group, which included all study personnel at all centres and the Steering Committee. These face-to-face meetings were valuable for creating and maintaining the enthusiasm of the investigators, as well as for discussing the study protocol and resolving possible discrepancies in interpretation across centres.

Annual site visits that included observation of study visits, individual meetings with each member of the study team and a review of monitoring data were initially conducted by the Study Chair and Director of the Co-ordinating Centre. After the first round of site visits, a clinician investigator was added to the site visit team, since the clinicians were more attuned to the details of the clinical protocol and could more easily observe whether the standard procedures were being followed. The information learned from visiting each centre could not have been obtained otherwise and was critical for evaluating standardisation of protocol.

Importance of a Good Clinic Co-ordinator

The importance of the role for a dedicated, organised, personable, detail-oriented study co-ordinator cannot be overemphasised. This person had the responsibility for maintaining ongoing contact with the parents and children, and had a strong influence on the attitude of the families towards the study. Therefore, the co-ordinator played a key role in retention of families and was the main communication link among the investigators within the clinical centre and with the Co-ordinating Centre. In addition, the co-ordinator was responsible for assuring that the data sent to the Co-ordinating Centre were complete and accurate.

Consideration of Child Safety Issues

Child safety was of paramount concern throughout the conduct of COMET. Before the trial was implemented, the DSMC reviewed and approved the protocol to ensure that there were no safety concerns. The major role of this committee during the conduct of the trial was to monitor the study data at least once a year for evidence of harmful, beneficial or no treatment effect. Based on the DSMC's recommendation at their first meeting, a 1-month follow-up visit was added to the protocol to evaluate eye muscle balance for the first group of COMET children enrolled. No significant child safety concerns were identified based on evaluation of the first 150 children and these visits were terminated. This visit was in addition to the 1-week and 3-month contacts already included in the protocol to monitor adaptability to the COMET glasses and to identify any safety issues.

Other steps included as part of the COMET protocol to ensure child safety involved routine monitoring of visual symptoms, inclusion of a mechanism for interim or problem visits to allow for prompt response to a child's problems, provision of eye care by a masked optometrist or, if necessary, an unmasked consulting optometrist, and safety of the lenses. Children and parents were questioned about visual symptoms at each visit to identify and address any visual problems. A protocol for problem visits was included that allowed for prompt attention to repair frames and lenses and to address any visual problems that had occurred between regular study visits. A mechanism that allowed for the unmasked consulting optometrists to schedule immediate consultation with clinicians from the other clinical centres, if necessary, was also incorporated into the protocol.

To address the safety of the COMET glasses, only polycarbonate lenses that met American National Standards Institute (ANSII) were used. In addition, single vision sports glasses meeting the ANSII standards and swim goggles were offered and their use encouraged for all children enrolled in COMET to protect against sports-related ocular injuries.

No serious study-related adverse events arose during COMET. However, several situations occurred which required referral to the consulting optometrist and that involved scheduling conference calls with the optometrists at the other clinical centres. The decision to change lens assignment from single vision lenses to PALs because of binocular vision problems in 2 children resulted from this process. The availability of the consulting optometrist and the protocol for consultation with clinicians from the other clinical centres proved to be quite valuable for such situations.

Flexible Recruitment Approach

One of the achievements of COMET was exceeding the study recruitment goal of 450 children within 1 year; it recruited an additional 19 children. The recruitment approach was flexible and varied at each centre according to its location within the city, affiliation with a larger university community and relationship with the local school systems. The centres based in university settings could draw from the university community and recruited the majority of their children from optometry clinic referrals and letters to parents of children wearing glasses, while the other centres emphasised recruitment from school screenings. After the recruitment goals were established, the number of children recruited, as well as the percentage of goal achieved at each centre and overall, was reported to all centres on a weekly basis. This created "friendly" competition among the centres and may have helped stimulate the recruitment process.

Commitment to High Retention

A high level of retention is essential to the success of any longitudinal study and that for COMET has been outstanding: 99% (462/469) of the children were followed for 3 years. Retention, which was routinely monitored, was a high priority for the COMET team. Specific steps taken to encourage high retention included administering a "COMET commitment" at each study visit, providing free eye care and spectacles, maintaining a good rapport with the families, maintaining contact with the families between visits through newsletters and other materials, providing toys and prizes at the visits, and encouraging an active role for the clinic co-ordinator. The "COMET commitment" described the families' responsibility to the study and was reviewed with the parents/guardians and children. They agreed to accept a random lens assignment, to have their child wear only COMET glasses and not contact lenses for at least 3 years and to call the clinic co-ordinator with any problems with the COMET glasses and questions about the study. The children also agreed to wear their COMET glasses during all waking hours.

One of the more important factors for high retention was the

close relationship that developed between the COMET staff and the families based on the high quality eye care and personalised attention given by the staff. The results of an ancillary study evaluating the specific reasons for the high level of retention will be presented in a separate report.

Necessity of Children's Adherence to the Protocol

Of equal importance and related to having excellent retention is having a high level of adherence to the protocol. To encourage adherence to the use of study glasses and to the visit schedule, the protocol provided back-up glasses and lens cleaning kits, identified opticians and optometrists outside of the clinical centre area to conduct interim visits for children who moved away, and provided transportation to return to the clinical centre for regularly scheduled visits. The high rate of wearing COMET glasses most or all the time (reported by the families) throughout the follow-up period and the low missed visit rate suggest that these approaches were useful in encouraging adherence.

Benefit of Examiner Certification, Standardisation and Ongoing Monitoring of Measurements

All study procedures were conducted according to a standard protocol that was documented in a detailed Manual of Procedures. At the study outset, before beginning data collection, a number of steps were taken to determine protocol-related decisions for study measurements and to train and certify study investigators. Pilot studies were conducted to determine the number of repeated measurements for cycloplegic and non-cycloplegic autorefraction, axial length and accommodation and phoria needed to achieve a balance between precision, efficiency and feasibility. The results provided a quantitative basis for these decisions based on the experience of COMET investigators using the COMET protocol and equipment.

Standard training of all investigators was provided at the first full study group meeting, where "gold standard" examiners trained the optometrists according to the study protocol for the measurements of cycloplegic autorefraction, axial length, accommodation and phoria. The opticians were trained to perform lensometry and to follow the fitting protocol for PALs. Prior to beginning data collection, all study investigators were certified according to specified criteria to perform all study measurements. These criteria involved setting limits for the variability of refractive error measurements by cycloplegic autorefraction, axial length measurements by A-scan and accommodation and phoria using a Canon R-1 to maximise the stability of the study measurements.

Since the investigators had limited experience taking ultrasound measurements prior to their participation in COMET, a pilot study was conducted among the study investigators to compare the 2 common methods for performing these measurements: slit lamp and hand-held methods. The results indicated that slit lamp measurements were more reliable and this approach was incorporated into the protocol as the method of choice. Additional analyses evaluated the baseline reliability of axial length measurements, which was excellent.[6]

Achieving standardisation of measurements is a challenge not just at baseline, but also during the follow-up period. The periodic site visits and evaluation of variability in protocol at different centres over time proved to be useful in evaluating fluctuations in adherence to the protocol. The Co-ordinating Centre routinely provided the COMET investigators with monitoring reports that included the evaluation of overall study progress and the reliability of the study measurements. Such information was useful for the study investigators to assess overall progress and to identify any issues that required immediate attention. With such close monitoring, standardisation was achieved.

Value of Inclusion of a Rule for Prescription Changes

The COMET protocol included the following rule to standardise the criteria for prescription changes: prescription changes are made when the difference in subjective refraction between the current and the most recent prescription (in at least 1 eye) is greater than or equal to 0.5D SE more myopia. Smaller prescription changes can be made if clinically indicated. All of these changes were documented and tracked. Having such a rule not only standardised the timing of prescription changes, but also provided a clinically meaningful measure of progression.

Value of Using Fourier Decomposition to Analyse Refractive Error

One analysis "lesson" is the positive value of analysing the progression of myopia by expressing refractive error as the sum of 3 components, M (mean spherical equivalent as described above), J_0 (dioptric power of a Jackson Cross Cylinder at axis, 0 degrees) and J_{45} (dioptric power of a Jackson Cross Cylinder at axis 45 degrees), as determined by the Fourier decomposition (rectangular form) method.[7] This approach was useful for creating an average refractive error value that includes all the refraction components for an individual and across individuals.

Significance of Maintaining Masking

COMET was designed as a double-masked clinical trial, in which neither the families nor the optometrists taking the study outcome measures were aware of the child's lens assignment. The preservation of masking in any clinical trial is important to minimise observation bias, particularly for the optometrists measuring study outcomes. The following steps were taken to preserve and monitor the masking of optometrists and families: including the consulting optometrist, mentioned previously, to handle any issues regarding visual symptoms; identifying children by a number unrelated to treatment assignment; providing verbal and printed instructions to the parents and children explaining that neither the family nor the COMET staff (other than the study optician, clinic co-ordinator and

consulting optometrist) were aware of the lens assignment, and emphasising the importance of not discussing any issues related to the study glasses with the COMET optometrists and not wearing study glasses in their presence; fitting glasses for and giving verbal instructions to all children as if each child had been assigned to PALs; standardising data collection forms and examination protocols for all children regardless of treatment assignment; giving the COMET glasses to the COMET optician or clinic co-ordinator for the duration of the study visit; requesting that each member of the COMET staff document any observed unmasking of the parents and children at each COMET visit; and monitoring whether the child or parent indicated knowledge of treatment assignment at each study visit.

At this point, the degree to which masking was maintained for the families and the optometrists is unknown. These data are being collected as part of the transition from a clinical trial to a longitudinal epidemiologic study and will be presented in a future report.

Conclusion

COMET was a multicentre, randomised, controlled clinical trial that evaluated the effect of progressive addition lenses versus single vision lenses on myopia progression in an ethnically diverse group of children from 4 centres in the US. The trial exceeded its recruitment goals, had excellent retention and achieved its aims by following children in their original lens assignment for at least 3 years. The study design incorporated standard features of clinical trial design that were beneficial to the study in meeting its goals. Additional design aspects were developed for COMET as a study evaluating treatment of a common eye condition conducted on healthy children. The experience with COMET has provided a number of valuable lessons for all aspects of the study design, ranging from selection of the members of the study team to creative methods for recruitment and retention, that should benefit the development and implementation of future clinical trials, particularly those done in similar populations of children. The use of a carefully designed protocol, using standard procedures by committed members of the study team, is essential to achievement of the study aims.

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