Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Pipeline

Five variables that rule your life – Home mortgage and biostatistical power

I was counseling a family member on the purchase of a home recently. This is particularly challenging in the highly priced Northern California real estate market in which we live. “I'm tired of throwing away my money on rent, and I don't get along with my landlord,” the family member said. “I want to start investing in a home”. I replied “I hear you, let's figure out how much you can afford.” They replied “I can afford a monthly payment of about what I am paying in rent”. I then asked “How much have you saved up for the down payment?” The answer was a figure far lower than one might have hoped. I said “There are 5 variables: the house price, down payment, interest rate and mortgage term which then determine your monthly payment”. This function is available on spreadsheet programs, typically called “PMT”, as well as on numerous websites.

I provide an illustration in Fig. 1. Given a “standard” mortgage term (30 years), and keeping the interest rate constant, the reader can see that indeed, the larger the down payment, the lower the monthly payment. The family member was rather depressed, realizing that dollar for dollar, the monthly payment would exceed their rent. I said “these are the 5 variables that rule your life as a homeowner”. I further went on to say that in the short-term, it costs more to own the same property you rent. I started to go into mortgage insurance that might be required for buyers with a proportionally low down payment, real estate taxes, home insurance, not to mention the need for an emergency fund for home repairs – but the person became visibly depressed.

This discussion of “five variables that rule your life” reminded me of the calculation of biostatistical power. As one who plans clinical studies of novel therapeutics, I frequently use this calculation to determine how big a study must be to have a chance to detect a potential treatment effect. Ironically, this calculation has five variables as well: the size of the treatment difference, the variability of the measurement, the alpha (chance of making a type 1 error – false positive), the beta (chance of making a type 2 error – false negative) which are used to calculate the fifth variable - the sample size. There are many programs to calculate power – SAS, nQuery and numerous web sites as well.

Many years ago, I wrote a review paper on novel β-adrenoceptor antagonists for the treatment of glaucoma and ocular hypertension [1]. At that time, there was a recently approved agent, and the sample size for a key published paper small (n = 20–25/group) [2]. The authors of that paper concluded that the new agent was similar in ocular hypotensive efficacy to timolol, the then standard. While that was true, the “power” of that statement of equivalency was low. In greater detail, in the subset of patients with monotherapy (n = 7–12/group) they found a 6.4 mm Hg decrease with timolol, and a 7.8 mm Hg decrease with the new agent, and concluded equivalency. While the observation is the observation, at the standard 80% power (an 80% chance to observe a difference of a given magnitude if it is truly there), they had the power to detect only a 4.0 mm Hg difference with the observed standard deviation of 3.0 mm Hg. Calculated from another perspective, in the monotherapy patients, the authors had only 40–55% power to detect a 2 mm Hg difference. A subsequent larger evaluation [3], and clinical practice studies found that the new agent was about 2 mm Hg less effective than timolol [3]. So, the initial small study did not have enough power to detect the “true effect”, and the comparative efficacy results of the pilot study were not borne out in larger studies.

The issue of power and sample size is a major one for evaluation of novel therapies in the treatment of dry eye. As noted in a previous article [4], the primary efficacy measure for some treatments is the proportion of patients responding (“categorical”), and for others is a mean sign or symptom (“continuous”). For example, how big would a study have to be to detect a difference between a cyclosporine product and vehicle of the magnitude of the cyclosporine products approved in the U.S., (5% in the vehicle group, and 15% in the active), it would have to have 141 patients per group. The sample size for this categorical analysis also depends upon the efficacy rate in the vehicle group. So if the vehicle group had a higher rate of responding (40%), in order to detect the same treatment effect (15%), then the sample size would be larger – 173 patients per group (Table 1).

A similar calculation for a vehicle-controlled study for a continuous measure, using the magnitude of efficacy of the other class of approved pharmacotherapy for dry eye (0.25 units on a 0–3 scale for inferior corneal fluorescein staining with a standard deviation 0.5), yields a sample size of 64/group (Table 1).

Fortunately we have several pharmacotherapies available in some countries, so it may be that future trials would be comparing two actives, rather than an active to a vehicle. A key step is to define the limits of equality. As I wrote in a previous column in this journal [5], this is called the non-inferiority margin. In the glaucoma example above, the non-inferiority margin in the 1980's and 1990's was 2 mm Hg [1]. Today, it is 1–1.5 mm Hg [6]. As I write this column, I am aware of only a few controlled studies of two active pharmacotherapies in dry eye. One is Downie et al., in which two formulations of an over-the-counter lubricant were compared. In this study of ~120 subjects per group, the authors found a difference in staining of 1.6 units (SD of 5–6) on a 0–30 scale, which was statistically significant. They interpreted it to be clinically significant [7]. This interpretation is one which will require further discussion in the ocular surface community.

That said, for power calculations, one might select a non-inferiority margin in dry eye studies of about 15%. For a categorical analysis, this might be detecting a difference of 12.75% vs 15.00%. For a continuous analysis, this might be detecting a difference of 0.038 units out of 0.250 units. The sample size would be 3705/group for categorical (15% response in active), 7705/group (55% response in active) and 2719/group for continuous (Table 1). Typically, a categorical analysis is less efficient on sample size than a continuous analysis, because in bifurcating the data (responder vs. non-responder), you are collapsing some of the details. Downie et al. [7] were fortunate to find statistical significance for a relatively small treatment effect (1.6 of 30 units, 5%); however, that is not always the case.

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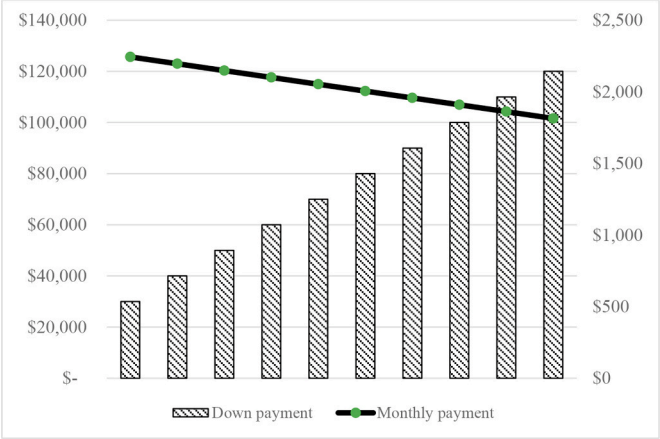

Fig. 1. Example of monthly mortgage payment (principal and interest) as a function of down payment.
Down payment is shown using the left hand axis, and monthly mortgage payment is shown using the right hand axis. Assuming $500,000 house, 4% interest rate and 30 year loan. Does not include real estate taxes, mortgage insurance, closing costs, or home insurance.

Table 1
Example of sample size calculations for dry eye therapeutic trials.

Categorical			Continuous		
Cases		N/group	Cases		N/group
Case 1: Vehicle controlled			Case 1: Vehicle controlled		
Vehicle response	5.00%	141	Treatment effect	0.25	64
Active response	15.00%		SD	0.50	
Case 2: Vehicle controlled					
Vehicle response	40.00%	173			
Active response	55.00%				
Case 3: Vehicle controlled			Case 3: Vehicle controlled		
Vehicle response	5.00%	50	Treatment effect	1.5	50
Active response	25.00%		SD	2.5	
Case 4: Active controlled			Case 4: Active controlled		
Vehicle response	12.75%	3705	Treatment effect	0.038	2719
Active response	15.0%		SD	0.500	
Case 5: Active controlled					
Vehicle response	52.75%	7705			
Active response	55.00%				

Assumptions: Power = 80%, alpha = 0.05, two-sided.
N/group = Number of patients required per group to achieve assumptions.
Categorical is the percent of patients responding (e.g., those with an increase in Schirmer score of 10 mm or more from baseline). Continuous is a mean (e.g., mean change in corneal staining, scale of 0 (none) to 15 (severe)). SD = Standard deviation.
Case 3 solves for a sample size of 50 per group, typical for a Phase 2 initial study.

As we noted in the TFOS DEWS II Clinical Trials report [8], power calculations such as the preceding are appropriate for pivotal studies as might be used for the regulatory approval of a new drug. They are also important for large public health trials such as those extramural trials sponsored by the National Institutes of Health (NIH). In the U.S., Europe and elsewhere, typically two confirmatory trials are required for approval. Thus, a power of 80% is traditional. NIH sponsored extramural trials tend to be singular, and thus a power of 90% is usually selected in sample size estimates. The higher the power, the larger the sample size.

Many novel therapeutics for the treatment of dry eye are sponsored by small firms that might be conducting an initial Phase 2 study to see if their novel agent is worthwhile of additional investment by the private sector. Sample sizes of the type needed for a study to demonstrate that the new treatment is at least as good as a current therapy are very daunting for the small firm. Indeed, even the sample sizes required for a vehicle-controlled study are challenging. The typical Phase 2 study for a novel dry eye product is about 50/group, based upon logistics and budget. One can see that the detection for treatment effect for such studies at 80% power is about 20% treatment effect for categorical analysis (5% vs 25%), and for continuous analysis approximately 10 points for SANDE (0–100 scale, assume standard deviation of 15 units) or about 1.5 units for total corneal staining (0–15 scale, assume standard deviation of 2.5 units).

In conclusion, the five variables for biostatistical power continue to rule the lives of those of us evaluating novel therapeutics for the treatment of ocular surface disease. For the small company evaluating novel therapies, logistical constraints mean that pilot studies will detect only those therapies with at least moderate treatment effects, and not those with only mild treatment effects. These studies also will typically be conducted in comparison to a negative control (e.g., vehicle). Further, the sample size requirements to detect differences between two active treatments mean that powerful studies can only be sponsored by institutions with large financial support, or that smaller studies will be of lower power in their comparison.

[SUBHEAD: caps and lower case] News from Pharmaceutical and Medical Device Companies.

Ophthalmic Products Related to the Ocular Surface Ophthalmic Products Not Related to the Ocular Surface Other News about Pharmaceutical and Medical Device Firms.

Government and public health news

- Acucela continues development of emixustat for the treatment of retinal degeneration based upon a recent publication [9] (December 2019), and press release regarding continued enrollment in a Phase 3 trial in patients with Stargardt disease (February 2020).
- Aerie announced that the European Medicines Agency (EMA) has accepted for review the marketing authorization application (MAA) for Roclanda (netarsudil and latanoprost ophthalmic solution, currently marketed as Rocklatan in the United States (January 2020).
- Aerpio announced results from the fifth cohort of subjects from a Phase 1b trial of a topical ocular formulation of AKB-9778 in patients with ocular hypertension (OHT) or primary open angle glaucoma (POAG, January 2020).
- Alcon received U.S. FDA approval for switching Pataday® (olopatadine) from prescription to over-the-counter (February 2020).
- Aldeyra started enrollment in its Phase 3 INVIGORATE Trial of topical ocular reproxalap in patients with allergic conjunctivitis. The

firm also started enrollment in a Phase trial of ADX-2191 (intravitreal methotrexate) for the prevention of recurrent retinal detachment due to proliferative vitreoretinopathy (January 2020).
- Allysta Pharmaceuticals started enrollment in a phase 1/2a trial of ALY688, a novel peptide agonist that binds to and activates adiponectin receptors, in patients with dry eye disease (January 2020).
- Dutch Ophthalmic Research Centre (DORC) received FDA approval for its Brilliant Blue for the visualization of internal limiting membranes (December 2019).
- EyeGate Pharma released results from a dry eye pilot study with its Ocular Bandage Gel (March 2020).
- Genentech and Roche started enrolled in a phase 3 trial of its Port Delivery System with ranibizumab (PDS) in people with diabetic macular edema (DME, January 2020).
- Graybug completed enrollment in its Phase 2b trial of its GB-10 intravitreal drug delivery system of sunitinib for the treatment of wet AMD.
- HanAll Biopharma and Daewoong Pharmaceutical announced topline results from the first US Phase 3 study of HL036 for treatment of dry eye (VELOS-2 study, January 2020).
- Horizon received FDA approval for its Tepezza™ (teprotumumab) as a treatment for thyroid eye disease (January 2020).
- Iveric announced results for its Zimura (avacincaptad pegol), a novel C5 inhibitor, in a phase 2b trial for the treatment of patients with geographic atrophy (GA) secondary to AMD. They also announced the design for a second trial (January 2020).
- Kala announced results from its Phase 3 STRIDE study evaluating KPI-121 0.25% (EYSUVIS™, loteprednol etabonate ophthalmic suspension) for the treatment of dry eye disease (March 2020).
- Leo Lens Pharma announced a notice of allowance from the U.S. Patent and Trademark Office for its proprietary MediPrint™ process for contact lens delivery of drugs (February 2020).
- Novartis received approval from the European Commission for its Beovu® (brolucizumab) for the treatment of wet age-related macular degeneration (AMD, (February 2020).
- Ocular Therapeutix presented results from its Phase 1, multi-centre, open-label, dose escalation clinical trial being conducted in Australia is intended to evaluate OTX-TKI, a tyrosine kinase inhibitor implant) for the treatment of wet AMD (March 2020).
- Oculis reported results from a phase 2 study of its OCS-01 (a novel eye drop formulation of dexamethasone) in patients with diabetic macular edema (DME, February 2020).
- Ocuphire entered into an agreement with Apexian Pharmaceuticals, Inc., granting Ocuphire an exclusive worldwide sublicense to Apexian's Ref-1 Inhibitor program, including its lead drug candidate APX3330, for all ophthalmic and diabetic indications (January 2020).
- Oyster Point Pharma announced the top-line results from its Phase 2 MYSTIC study of OC-01 (in Dry Eye Disease (January 2020) [10].
- ProQR received rare pediatric disease designation for its QR-421a RNA-based oligonucleotide for the treatment of Usher Syndrome (January 2020). The firm also announced results from its Phase 1/2 study (March 2020).
- Santen cleared a regulatory hurdle to make its Verkazia® (cyclosporine) available for patients with severe vernal keratoconjunctivitis in Quebec (January 2020).
- Tetra Bio-Pharma received orphan drug designation from the U.S. FDA for its cannabinoid PPP003 to prevent proliferative vitreoretinopathy (April 2020).

Gene therapy

- Adverum dosed the first patient in cohort 4 of phase 1 OPTIC trial of intravitreal ADVM-022, a vector capsid for aflibercept (April 2020).
- Applied Genetic Technologies Corporation reported interim six-month data from its ongoing Phase 1/2 clinical program in X-linked retinitis pigmentosa (XLRP, January 2020).
- Editas announced treatment of a patient with intraocular CRISPR gene editing to treat a patient with a retinal degeneration (March 2020).
- Lineage Cell Therapeutics provided an update on its ongoing Phase 3 study for the treatment of dry age-related macular degeneration of OpRegen, a retinal pigment epithelium transplant therapy delivered subretinally using a delivery system from Gyroscope Therapeutics (February 2020).
- Regenxbio announced results from an ongoing Phase 1/2a trial of its RGX-314 gene therapy for wet AMD (April 2020).

Regulatory, government, and pharmaceutical industry

- Alexion completed its acquisition of Achillion (January 2020).
- Santen Pharmaceutical and the Alphabet subsidiary, Verily announced the establishment of a joint venture focused on applying microelectronics and scalable digital technologies to ophthalmology (February 2020).
- A growing number of states are proposing laws to ban cosmetics the safety of which is testing on animals prior to marketing. Animal-tested cosmetics already are banned in Europe, India and elsewhere (January 2020).
- The practice of dispensing 90-days of medication, efficient for healthcare delivery, was questioned for patients with depressive disorders, as it may provide them an easily available method to commit suicide [11].
- There is a growing realization that sponsors of clinical trials are not complying with the law regarding posting of results on clinicaltrials.gov. The apparent non-compliers include academic, government and industry-sponsored studies (January 2020) [12].
- A number of drugs are projected to lose exclusivity in the U.S. in 2020, the top ten of which had $8 billion in 2019 U S. sales (March 2020).
- Roche is supplying its arthritis drug Actemra® (tocliziumab) to doctors treating patients with COVID-19 infections. Note that this use is investigational (March 2020).
- The University of California and the Public Library of Science (PLOS) announced a two-year agreement that will make it easier and more affordable for UC researchers to publish in the nonprofit open access publisher's suite of journals (February 2020).
- In this review period, the FDA:
  - Released a guidance for Human Gene Therapy for Retinal Disorders (January 2020).
  - Conducted of a study on brand names of drugs with respect to how they influence consumers' and healthcare providers' perceptions, and may overstate efficacy (January 2020) [13].
  - Published a cumulative dataset on approved new molecular entities (drug and biologic) approvals from 1985 to 2019 (March 2019).
- The COVID-19 pandemic has had a major impact on government regulation and ophthalmic practice and research. Selected items of interest include:
  - The ophthalmic and medical community is recognizing the role played by Dr. Li Wenliang, ophthalmologist, of Wuhan, China, for his early work in identifying the clinical signs and symptoms of the COVID-19 virus (March 2020) [14].
  - A group of leaders in the retinal ophthalmic pharmaceutical industry issued a joint statement on prioritizing patient safety for patients in trials of therapies for retinal diseases at this time of the COVID pandemic, including minimizing study visits and enrollment of new patients (Genentech, Boehringer Ingelheim, Kodiak Sciences, Apellis Pharmaceuticals, Graybug Vision, Bayer, Adverum, Novartis and REGENXBIO; March 2020).
  - The FDA issued a statement regarding the pragmatic challenges of conducting clinical trials, especially considering the American

Academy of Ophthalmology recommendation to limit patient interaction to urgent care (March 2020).

- The U.S. Federal leadership discussed using “re-purposing” of molecules approved for other indications, and the rubric “it couldn't hurt”. These development pathways and concerns have been addressed previously [15–17].
- A controlled trial of lopinivar-ritonavir in adults with severe COVID-19 showed no benefit [18]. Chloroquine was reported effective in an open-label trial in the treatment of COVID-19, [19] however, the International Society of Antimicrobial Chemotherapy subsequently stated that the article “does not meet the [society's] expected standard, especially relating to the lack of better explanations of the inclusion criteria and the triage of patients to ensure patient safety.” [20].
- Continuing to facilitate development of treatments, the FDA including a statement (as of March 19, 2020) that “While there are no FDA-approved therapeutics or drugs to treat, cure or prevent COVID-19, there are several FDA-approved treatments that may help ease the symptoms from a supportive care perspective”
- FDA expressed concern regarding therapeutic products that are derived from human cells, tissues or cellular or tissue-based products (HCT/Ps) related to the ongoing COVID-19 (corona virus) outbreak (February 2020).
- FDA postponed all foreign inspections due to the COVID-19 pandemic (March 2020). In a related article, this has challenged the U.S. reliance on foreign drug manufacture, estimated as 40% of finished medications and 80% of active pharmaceutical ingredients (April 2020) [21].
- Cepheid's point-of-care diagnostic for COVID-19 was authorized for use by the U.S. FDA (March 2020).
- FDA is expediting clinical trials for diagnosis and treatment, albeit with continued concern for patient safety (March 2020).
- FDA declared a public health service emergency authorizing emergency use of in vitro diagnostics for detection and/or diagnosis of COVID-19.
- FA expanded the availability and capability of non-invasive remote monitoring devices to facilitate patient monitoring (March 2020).
- FDA temporarily allowed compounding of selected medications (April 2020).
- FDA converted planned in-person meetings to teleconferences (April 2020)
- FDA an emergency use authorization for the investigational antiviral drug remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease (May 2020).

Disclosure

Gary D. Novack, Ph.D. consults with numerous pharmaceutical and medical device firms.

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