Special Issue

Decade-Long Profile of Imaging Biomarker Use in Ophthalmic Clinical Trials

Edoardo Villani,[1] Domenico Massaro,[1] Matteo Scaramuzzi,[1] Pedram Hamrah,[2] Felipe A. Medeiros,[3] and Paolo Nucci[1]

[1]Department of Clinical Sciences and Community Health, University of Milan, Eye Clinic San Giuseppe Hospital, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Multimedica, Milan, Italy
[2]Department of Ophthalmology, Cornea Service and Boston Image Reading Center, Tufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts, United States
[3]Hamilton Glaucoma Center, Visual Performance Laboratory, University of California San Diego, La Jolla, California, United States

Correspondence: Edoardo Villani, Department of Clinical Sciences and Community Health, University of Milan, Eye Clinic San Giuseppe Hospital, via San Vittore 12, 20123 Milan, Italy; edoardo.villani@unimi.it.

Submitted: March 1, 2017
Accepted: April 18, 2017

Citation: Villani E, Massaro D, Scaramuzzi M, Hamrah P, Medeiros FA, Nucci P. Decade-Long profile of imaging biomarker use in ophthalmic clinical trials. *Invest Ophthalmol Vis Sci*. 2017;58:BIO76–BIO81. DOI: 10.1167/iovs.17-21790

Purpose. The purpose of this study was to investigate the use of imaging biomarkers in published clinical trials (CTs) in ophthalmology and its eventual changes during the past 10 years.

Methods. We sampled from published CTs in the fields of cornea, retina, and glaucoma between 2005–2006 and 2015–2016. Data collected included year of publication, phase, subspecialty, location, compliance with Consolidated Standards for Reporting Trials, impact factor, presence and use of imaging biomarkers (diagnostic, prognostic and predictive; primary and secondary surrogate endpoints), and use of centralized reading centers.

Results. We included 652 articles for analysis, equally distributed in three timeframes (2005–2006, 2010–2011, and 2015–2016), mainly reporting phase IV CTs and trials on procedures (42.2% and 35.4%, respectively). Imaging biomarkers were included in 46.3% of the analyzed CTs and their use significantly increased over time ($P < 0.05$). Optical coherence tomography was the most frequently used device (27.7%), whereas diagnostic biomarkers and secondary surrogate endpoints were the most frequent biomarker types (19.5% and 22.5%, respectively). Early-phase CTs showed an increase in the use of biomarkers for patient selection and stratification over time ($P < 0.05$), but not in the use of imaging surrogate endpoints ($P = 0.90$). Only 3 of 59 (5.1%) of phase III CTs included primary surrogate imaging endpoints, whereas secondary surrogate imaging endpoints were present in 50.8% of these trials ($P < 0.001$). Retinal CTs had the highest prevalence for each type of imaging biomarker ($P < 0.001$). Reading centers were used in 52 of 302 CTs (17.2%), with no significant time-related increase.

Conclusions. Imaging biomarkers are increasingly used in published CTs in ophthalmology. Additional efforts, including centralized reading centers, are needed to improve their validation and use, allowing a wider use of these tools as primary surrogate endpoints in phase III CTs.

Keywords: imaging, clinical trials, biomarker, surrogate endpoint, ophthalmic research

The National Institutes of Health Biomarkers Definitions Working Group defined *biomarker* as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[1] More than 10 years ago, in the white paper titled "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products,"[2] the Food and Drug Administration recognized the critical role of biomarkers in drug development.

At present, there is broad consensus among researchers and regulatory agencies regarding the importance of biomarkers to translate scientific concepts into diagnostic and therapeutic approaches and technologies.[3] They represent an essential set of tools for accelerating basic science, drug discovery, and medical product development as well as improving clinical care.[3]

Biomarkers are generally used for two main indications in clinical research. First, to select and stratify the study population (diagnostic, prognostic, and predictive biomarkers) and second, to replace true clinically relevant endpoints (surrogate endpoints) predicting the clinical benefit or harm of interest.[1,4,5]

The use of biomarkers as surrogate endpoints in very early phases of clinical trials (CTs) to provide proofs of concept is of obvious utility. However, their inclusion in phase III CTs, where potential erroneous decisions based on invalid surrogate endpoints may have broad public health consequences, may pose specific and important challenges.[1,6,7]

Medical imaging is increasingly used for screening, diagnosis, prognosis, evaluating the natural history of disease, or monitoring therapeutic efficacy. An imaging biomarker specifically uses a characteristic that is objectively observed and measured using an imaging device. The potential advantages of this approach are the chance to minimize subjective bias and inaccuracy as a result of unclear measurements, the ability to

reveal subtle subclinical features or changes, and the opportunity to have blinded, standardized, and centralized evaluation of the images.[8–11]

The past 2 decades have seen a revolution in ophthalmic imaging, with a near exponential rise in peer-reviewed publications relating to clinical applications of new imaging modalities.[12] More important, this revolution has now reached CT design in ophthalmology.[11] Thus, we hypothesized that increased usage of imaging biomarkers in ophthalmic clinical research has occurred during the past 10 years. The purpose of this observational retrospective study was to verify this hypothesis, analyzing the use of imaging biomarkers in published CTs in ophthalmology and its relative utility during the past decade.

Methods

We searched Medline through PubMed for CTs on cornea, glaucoma, and retina published in three different time periods from 2005 to 2016. Using filter tools provided by the website, we selected "Clinical trial" OR "Randomized controlled trial" as article type; "from 2005/07/01 to 2006/06/30," "from 2010/07/01 to 2011/06/30," and "from 2015/07/01 to 2016/06/30" as publication dates; and "Cornea OR Glaucoma OR Retina" as keywords. Two investigators (DM, MS) independently analyzed the full text of each paper and assessed the inclusion and exclusion of trials on the basis of topic (related to cornea, glaucoma, or retina), of article type (adherent to the World Health Organization definition of Clinical Trial),[13] and of language (we included English-language papers only). Disagreements were settled by discussion with a third investigator (EV).

Data collected for each included article consisted of the following features: Digital Object Identifier (DOI) of the article, publication timeframe (2005–2006, 2010–2011 or 2015–2016), phase (I/II, III, IV, or trials on procedures), subspecialty (cornea, glaucoma, or retina), location (geographical area of the coordinating site), compliance with Consolidated Standards for Reporting Trials (CONSORT) guidelines[14] (yes if >12 items were fully reported; no if <12 items were fully reported), and impact factor (impact factor of the journal in which the study was published).[15]

Moreover, articles were analyzed to detect the use of imaging biomarkers in general (yes or no), imaging diagnostic biomarkers (yes or no), imaging prognostic biomarkers (yes or no), imaging predictive biomarkers (yes or no), imaging surrogate primary endpoints (yes or no), and imaging surrogate secondary endpoints (yes or no) and to assess the use of a centralized reading center (RC). Biomarker types were defined on the basis of the Food and Drug Administration–National Institutes of Health BEST Resource.[5]

Statistical analysis was conducted with commercial software (SPSS for Windows, version 21.0; SPSS Sciences, Chicago, IL, USA). Categorical data were expressed as "ratios (percentages)," impact factor as mean ± standard deviation. Changes over the three timeframes were analyzed by linear-by-linear association trend test. Percentages were compared by χ^2 test (with appropriate number of degrees of freedom, depending on contingency table size), and the impact factor was compared by Mann-Whitney *U* test (between two groups) or by Kruskal-Wallis test (more than three groups). The α level (type I error) was set at 0.05.

Results

The Medline search provided 1130 articles (367, 388, and 375 in 2005–2006, 2010–2011, and 2015–2016, respectively). After detailed assessment of article methodology, we included 652 papers for analysis (190, 231, and 231 in 2005–2006, 2010–2011, and 2015–2016, respectively; Table 1). The 478 excluded articles included 70 that were out of scope, 332 studies other than clinical trials, and 76 written in languages other than English.

The percentage of phase IV CTs and trials on procedures (275 of 652 [42.2%] and 231 of 652 [35.4%], respectively) was significantly higher than phase I/II or III trials (87 of 652 [13.3%] and 59 of 652 [9.0%], respectively); $P < 0.001$.

Comparing the clinical trial phase distribution over the three timeframes studied, we found a progressive increase in phase III CTs (2 of 190 [1.1%] vs. 19 of 231 [8.3%] vs. 38 of 231 [16.4%]), and a progressive decrease in phase IV CTs (108 of 190 [56.8%] vs. 92 of 231 [40.0%] vs. 75 of 231 [32.3%]), in 2005–2006, 2010–2011, and 2015–2016, respectively; $P < 0.001$.

No difference in the number of included articles was found when grouping the articles on the basis of subspecialty: 203 of 652 (31.1%) vs. 208 of 652 (31.9%) vs. 241 of 652 (37.0%), respectively, for cornea, glaucoma, and retina; $P = 0.14$.

Retinal CTs significantly increased in 2010–2011 and 2015–2016 (95 of 231, 41.3%, and 90 of 231, 38.8%) compared to 2005–2006 (56 of 190, 29.5%); $P < 0.05$ in both cases.

Retinal studies included most of the phase III CTs (50 of 59 [84.7%]), and the percentage of phase III CTs in retina progressively increased over time from 1 of 56 (1.8%) in 2005–2006 to 16 of 95 (16.8%) in 2010–2011, to 33 of 90 (36.7%) in 2015–2016; $P < 0.001$ (Table 2).

Phases I/II and III were minimally represented in cornea and glaucoma subspecialties (20 of 203 [9.8%] and 11 of 208 [5.3%], respectively). Trials on procedures and phase IV studies were the most frequent, respectively, in cornea (123 of 203 [60.6%]; $P < 0.001$) and glaucoma (135 of 208 [64.9%]; $P < 0.001$) subspecialties (Tables 3, 4).

Grouping the articles on the basis of geographical regions, 91.9% of published CTs were from North America (204 of 652, 31.3%), Europe (228 of 652, 35.0%), and Asia (167 of 652, 25.6%). CTs from Asia progressively increased from 2005–2006, to 2010–2011, and to 2015–2016 (34 of 190 [17.9%], 52 of 231 [22.6%], and 81 of 231 [34.9%], respectively); $P < 0.001$.

The percentage of articles compliant with CONSORT guidelines (393 of 652 [60.3%]) did not show a significant progressive change over time: 99 of 190 (52.1%) in 2005–2006, 158 of 231 (68.4%) in 2010–2011, and 136 of 231 (58.9%) in 2015–2016; $P = 0.24$. The mean impact factor of journals publishing the included CTs progressively increased from 2.08 ± 1.28 in 2005–2006 to 3.28 ± 4.90 in 2010–2011, and to 3.34 ± 4.30 in 2015–2016, $P < 0.001$. The impact factor of CONSORT compliant articles was significantly higher (3.55 ± 4.92 vs. 2.04 ± 1.27); $P < 0.001$.

In this analysis, the published CTs including imaging biomarkers were 302 of 652 (46.3%). Tables 5 and 6 report, respectively, the most commonly used imaging devices and the imaging parameters most frequently used as biomarkers.

Over the three timeframes, we found a significant time-related increase of imaging biomarkers usage: 74 of 190 (38.9%) in 2005–2006, 113 of 231 (48.9%) in 2010–2011, and 115 of 231 (49.8%) in 2015–2016, $P < 0.05$. A similar significant trend was also found limiting the analysis to imaging biomarkers used for patient selection and stratification (including predictive, diagnostic, and prognostic): 31 of 190 (16.3%) in 2005–2006, 55 of 231 (23.8%) in 2010–2011, and 67 of 231 (29.0%) in 2015–2016; $P < 0.01$ (Table 7).

Early-phase CTs (phases I/II and III) showed a significant increase over time in the use of biomarkers for patient selection and stratification (including predictive, diagnostic

Table 1. Features of Included Published Clinical Trials

Assessed Features	7/2005–6/2006	7/2010–6/2011	7/2015–6/2016	Total
Number of papers	190	231	231	652
Phases				
I–II	12	45	30	87
III	2	19	38	59
IV	108	93	74	275
Trials on procedures	68	74	89	231
Subspecialty				
Cornea	66	65	72	203
Glaucoma	68	71	69	208
Retina	56	95	90	241
Geographical area				
North America	55	80	69	204
South America	9	10	6	25
Europe	86	79	63	228
Asia	34	52	81	167
Oceania	5	5	3	13
Africa	1	4	10	15
CONSORT compliance				
Yes	99	158	136	393
No	91	72	96	259
Impact factor	2.08 ± 1.28	3.28 ± 4.90	3.34 ± 4.30	2.95 ± 3.97

CONSORT, Consolidated Standards for Reporting Trials.

and prognostic): 5 of 14 (35.7%) in 2005–2006, 30 of 64 (46.9%) in 2010–2011, and 42 of 68 (61.8%) in 2015–2016; $P < 0.05$. The same analysis performed on surrogate imaging endpoints (including both primary and secondary endpoints) showed no significant growth over the three timeframes; $P = 0.90$.

Although 30 of 59 (50.8%) of phase III CTs used secondary surrogate imaging endpoints, we found only 3 of 59 (5.1%) phase III CTs including primary surrogate imaging endpoints: two on retina[16,17] (macular thickness by optical coherence tomography [OCT] and lesion enlargement by fundus autofluorescence) and one on glaucoma[18] (iris color photography). Conversely, phase IV CTs included primary surrogate imaging endpoints in 75 of 275 (27.2%) cases; $P < 0.001$.

Furthermore, grouping the trials on the basis of subspecialty, the retina field demonstrated a higher percentage of CTs that included imaging biomarkers, as compared to both cornea and glaucoma (186 of 241 [77.2%] vs. 75 of 203 [36.9%] vs. 41 of 208 [19.7%], respectively); $P < 0.001$. Repeating the same analysis, considering each type of biomarker separately, retinal CTs showed the highest prevalence of imaging biomarkers in any case (Table 8).

Centralized RCs were used in 52 of 302 CTs (17.2%), with no significant time-related increase: 8 of 74 (10.8%) vs. 25 of 113 (22.1%) vs. 19 of 115 (16.5%), respectively, in the three timeframes; $P = 0.13$. We found a significant higher presence of RCs in retina CTs (48 of 186, 25.8%) when compared with the other subspecialties (0 of 75 and 4/41 [9.8%], respectively, in cornea and glaucoma); $P < 0.001$. Grouping by phases, RCs were used in 21 of 48 (43.8%) of phase III CTs, 14 of 64 (21.9%) of phase I/II, 17 of 108 (15.7%) of phase IV, and 0 of 82 in CTs on procedures; $P < 0.001$.

The mean impact factor related to articles reporting CTs including imaging biomarkers was significantly higher (3.60 ± 5.57) when compared with those without imaging biomarkers (2.40 ± 1.42); $P < 0.001$. Similarly, research articles including RCs were published in journals with higher impact factors (5.94 ± 8.83 vs. 3.11 ± 4.49; $P < 0.05$).

CONSORT-compliant reports showed a significantly higher percentage of trials including at least one imaging biomarker (212 of 393 [53.9%] vs. 90 of 259 [34.7%]); $P < 0.001$. Interestingly, CTs on retina showed the best CONSORT compliance (173 of 241 [71.8%]) when compared with the two other subspecialties (117 of 203 [57.6%] and 103 of 208 [49.5%] for cornea and glaucoma, respectively; $P < 0.001$).

Discussion

The inclusion of imaging biomarkers in ophthalmic clinical research shows great promise and, on the basis of our data, these tools are included in almost half of the ophthalmic clinical trials published in the past 10 years. We found a

Table 2. Main Features of Published Retinal Clinical Trials

Retina	2005–2006	2010–2011	2015–2016	Total
Number of papers	56	95	90	241
Phases				
I–II	5	36	24	65
III	1	16	33	50
IV	36	26	18	80
Trials on procedures	14	17	15	46

Table 3. Main Features of Published Corneal Clinical Trials

Cornea	2005–2006	2010–2011	2015–2016	Total
Number of papers	66	65	72	203
Phases				
I–II	7	7	2	16
III	0	0	4	4
IV	19	22	19	60
Trials on procedures	40	36	47	123

Table 4. Main Features of Published Glaucoma Clinical Trials

Glaucoma	2005–2006	2010–2011	2015–2016	Total
Number of papers	68	71	69	208
Phases				
I–II	0	2	4	6
III	1	3	1	5
IV	53	45	37	135
Trials on procedures	14	21	27	62

significantly increasing use of imaging biomarkers in general as tools for patient selection and stratification (mostly diagnostic biomarkers) and as secondary surrogate endpoints. The large use of imaging biomarkers requires efforts aimed to their standardization, rigorous validation, and adequate use as part of high-quality and well-designed clinical studies as well as the utility of centralized RCs.

For early-phase studies, we reported a high increase in the percentage of CTs including imaging biomarkers, other than surrogate endpoints, in the past 10 years. Given regulatory and broad public health implications, the inclusion of primary surrogate imaging endpoints in phase III CTs has particular challenges, starting from the need for appropriate validation and qualification processes. As recently discussed by Wagner and Atkinson,[6] validation is the process of assessing the assay and its measurement performance characteristics and determining the range of conditions under which the assay will give reproducible and accurate data. Qualification, essential for surrogate endpoints, is the "fit for purpose" process aimed to demonstrate not only the link between a biomarker and a biological process but also that, "within the stated context of use, a biomarker can be relied upon to have a specific interpretation and application in drug development and regulatory review."[4,19]

Furthermore, the use of imaging data as a primary endpoint in CTs requires particular attention to the need for trial-specific imaging process standards and for centralized, blinded imaging interpretation by RCs.[11]

Centralized RCs guarantee collection of high-quality, standardized, and unbiased imaging data that are uniform across different clinical sites and masked to any clinical information.[20] Our data showed that CTs including imaging biomarkers assessed by centralized RCs were published in journals with a higher impact factor, suggesting that these research articles might obtain broader consideration. Moreover, RCs were mostly used in phase III CTs, which have more stringent regulatory requirements. Our failure to demonstrate a time-related increase in the use of RCs suggests the need for huge commitment to the improvement of imaging biomarkers usage in clinical research.

Table 5. Most Commonly Used Imaging Devices by Subspecialty

Retina, $n = 241$	Cornea, $n = 203$	Glaucoma, $n = 208$
OCT, 152 (63.1)	Corneal topography, 29 (14.3)	Color photography, 14 (6.7)
FAG, 82 (34.0)	AS-OCT, 16 (7.9)	OCT, 13 (6.3)
Color photography, 19 (7.9)	In vivo confocal microscopy, 13 (6.4)	Doppler ultrasound, 7 (3.4)
Autofluorescence, 9 (3.7)	External color photography, 6 (2.9)	GDx, 5 (2.4)

Data are expressed as number of observed cases (percentage). OCT, optical coherence tomography; FAG, fluorescein angiography; AS-OCT, anterior segment optical coherence tomography; GDx, scanning laser polarimetry.

Table 6. Imaging Parameters Most Commonly Used as Biomarkers by Subspecialty

Retina, $n = 241$	Cornea, $n = 203$	Glaucoma, $n = 208$
Central macular thickness by OCT, 113 (46.9)	Central corneal thickness by topography, 8 (39)	Optic nerve disc morphology by color photograph, 6 (2.9)
Leakage by fluorescein angiography, 39 (16.2)	Central corneal thickness by OCT, 6 (3.0)	Anterior chamber volume by OCT, 4 (1.9)
Lesion size by fluorescein angiography, 18 (7.5)	Corneal cone apex (Kmax) by topography, 10 (4.9)	Anterior chamber volume by ultrasound biomicroscopy, 2 (1.0)
Hyporeflective subretinal space by OCT linear scan, 12 (5.0)	Endothelial cell density by Specular microscopy, 5 (205)	Systolic and diastolic peak velocity by Ecocolor doppler, 6 (2.9)
Hyporeflective intraretinal cavities by OCT linear scan, 3 (12)	Subbasal nerve fiber layer by confocal microscopy, 4 (2.0)	RNFL by OCT, 2 (1.0)
	Ketocyte cell density by confocal microscopy, 4 (2.0)	RNFL by GDx, 2 (1.0)
		Bleb Morphology by color photography, 3 (1.4)

Data are expressed as number of observed cases (percentage). OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; GDx, scanning laser polarimetry.

Table 7. Trend of Imaging Biomarkers Use Over Time

Biomarkers' Classes	2005–2006, $n = 190$	2010–2011, $n = 231$	2015–2016, $n = 231$	*P* Value	Total, $n = 652$
Trials including at least 1 imaging biomarker	74 (38.9)	113 (48.9)	115 (49.8)	<0.05	302 (46.3)
Diagnostic imaging biomarker	30 (15.8)	40 (17.3)	57 (24.7)	<0.05	127 (19.5)
prognostic imaging biomarker	1 (0.5)	4 (1.7)	12 (5.2)	<0.01	17 (2.6)
Predictive imaging biomarker	9 (4.7)	22 (9.5)	15 (6.5)	0.56	46 (7.1)
Primary surrogate imaging endpoint	28 (14.7)	37 (16.0)	30 (13.0)	0.51	95 (14.6)
Secondary surrogate imaging endpoint	24 (12.6)	59 (25.5)	64 (27.7)	<0.001	147 (22.5)

Data are expressed as number of observed cases (percentage). *P* by linear-by-linear association test.

Table 8. Comparison of Prevalence of Imaging Biomarkers Use by Subspecialty

Biomarkers' Classes	Retina, $n = 241$	Cornea, $n = 203$	Glaucoma, $n = 208$	*P* Value
Trials including at least 1 imaging biomarker	186 (77.2)	75 (36.9)	41 (19.7)	<0.001
Diagnostic imaging biomarker	106 (44.0)	12 (5.9)	9 (4.3)	<0.001
Prognostic imaging biomarker	12 (5.0)	2 (1.0)	3 (1.4)	<0.01
Predictive imaging biomarker	36 (14.9)	7 (3.4)	3 (1.4)	<0.001
Primary surrogate imaging endpoint	52 (21.6)	27 (13.3)	16 (7.7)	<0.001
Secondary surrogate imaging endpoint	102 (42.3)	28 (13.8)	17 (8.2)	<0.001

Data are expressed as number of observed cases (percentage). *P* by χ^2 test.

Major efforts are needed to avoid the potential consequences of biomarker misuse or of the choice of invalid surrogate endpoints (ranging from the approval of a therapy favorably affecting the surrogate but not the clinical endpoint[21] to the failure of trials because of underpowering or poor patients selection[22]). On the other hand, it is essential to allow imaging biomarkers to play a central role in supporting new drugs development and approval. Our data highlight these concerns, showing a persistent almost total lack of primary surrogate imaging endpoints in phase III CTs to date.

In our analysis, phase IV CTs showed a significantly higher presence of primary surrogate imaging endpoints (27.2%). This finding may be because of the very high utility of this approach in postmarketing trials, which require less stringent validation and allow a less risky and more pioneering use of biomarkers to demonstrate their proof of concept. However, standardization and validation are also important in phase IV CTs because, as stated by Ioannidis in the controversial article titled "Why Most Published Research Findings Are False,"[23] "the greater the flexibility in designs, definitions, outcomes, and analytical modes in a scientific field, the less likely the research findings are to be true."[23]

The subspecialty-based analysis revealed that retinal CTs had the highest prevalence of every type of imaging biomarker, mainly because of the wide use of OCT (included in 27.7% of all the analyzed CTs and in 63.1% of CTs on retina). Fujimoto and Swanson recently highlighted the dramatic growth in OCT-related publications during the past years, indicating the extent of scientific and clinical progress due to this technology.[24] Moreover, in the past 10 years, the pivotal role of OCT imaging in the development of anti-angiogenic therapies for the treatment of macular diseases provided a remarkable example of the potentials of synergy between imaging technologies and pharmaceutical research in ophthalmology.[25]

Another interesting result is that articles reporting retinal CTs showed the most frequent use of RCs and the highest CONSORT compliance. Given the well-known suboptimal adherence to these standards in published trials,[26–28] we arbitrarily defined as compliant the articles fully reporting more than one half of the items included in the CONSORT checklist.[14] Although not a direct measure of the intrinsic quality of a study, reporting quality provides the reader with useful tools for the evaluation of its validity.

The present study provides new preliminary information on ophthalmic implications of a hot topic in clinical research. However, our study has some limitations. The methodology used for search and inclusion of articles is partially arbitrary and provided a relatively small sample of articles, particularly of phase III trial reports. Moreover, as it is based on already published and indexed reports, this study does not include the most recently designed CTs and might not fully reflect the very last state of imaging use in clinical research.

In conclusion, this study shows a large use of imaging biomarkers in published CTs in ophthalmology and an increase in the use of imaging biomarkers for patient selection and stratification and as secondary surrogate endpoints. Additional efforts are needed to improve validation of these tools to overcome infrastructural, economic, and cultural obstacles,[29] optimizing the use of imaging biomarkers in clinical research and allowing more frequent use of imaging surrogate primary endpoints to support new drug development and approval.

Acknowledgments

Disclosure: **E. Villani**, Allergan (C), FB Vision (C), Bausch & Lomb (R); **D. Massaro**, None; **M. Scaramuzzi**, None; **P. Hamrah**, Allergan (C), CooperVision (C), Shire (C), GlaxoSmithKline (C), Dompe (C), Bausch & Lomb (C), Revision Optics (C), Eyegate Pharmaceuticals (C), Heidelberg Engineering (C), Tissue-Tech (C), Aeri Pharmaceutics (C), Santen, Inc. (C), Stemnion (C); **F.A. Medeiros**, Carl-Zeiss Meditec (F), Heidelberg Engineering (F), Reichert (F), Topcon (F); **P. Nucci**, Thea (R), Bayer (R), Sooft (R)

References

1. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69:89–95.
2. U.S. Department of Health and Human Services. Innovation/Stagnation: Challenges and Opportunities on the Critical Path to New Medical Products. Available at: http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM113411.pdf. Accessed January 5, 2017.

3. Robb MA, McInnes PM, Califf RM. Biomarkers and surrogate endpoints: developing common terminology and definitions. *JAMA*. 2016;315:1107–1108.
4. Amur S, LaVange L, Zineh I, Buckman-Garner S, Woodcock J. Biomarker qualification: toward a multiple stakeholder framework for biomarker development, regulatory acceptance, and utilization. *Clin Pharmacol Ther*. 2015;98:34–46.
5. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. Available at: http://www.ncbi.nlm.nih.gov/books/NBK326791/. Accessed February 14, 2017.
6. Wagner JA, Atkinson AJ Jr. Measuring biomarker progress. *Clin Pharmacol Ther*. 2015;98:2–5.
7. Medeiros FA. Biomarkers and surrogate endpoints in glaucoma clinical trials. *Br J Ophthalmol*. 2015;99:599–603.
8. Mankoff DA, Farwell MD, Clark AS, Pryma DA. How imaging can impact clinical trial design: molecular imaging as a biomarker for targeted cancer therapy. *Cancer J*. 2015;21:218–224.
9. Eckstein F, Guermazi A, Gold G, et al. Imaging of cartilage and bone: promises and pitfalls in clinical trials of osteoarthritis. *Osteoarthr Cartil*. 2014;22:1516–1532.
10. Razzouk L, Farkouh ME. Imaging outcomes in cardiovascular clinical trials. *Nat Rev Cardiol*. 2009;6:524–531.
11. U.S. Department of Health and Human Services. Clinical Trial Imaging Endpoint Process Standards: Guidance for Industry. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm268555.pdf. Accessed February 14, 2017.
12. Ilginis T, Clarke J, Patel PJ. Ophthalmic imaging. *Br Med Bull*. 2014;111:77–88.
13. Kao LS, Tyson JE, Blakely ML, Lally KP. Clinical research methodology I: introduction to randomized trials. *J Am Coll Surg*. 2008;206:361–369.
14. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c869.
15. Journal Citation Report. Thomson Reuters website. Available at: http://admin-apps.webofknowledge.com.pros.lib.unimi.it/JCR/JCR. Accessed February 14, 2017.
16. Moradian S, Faghihi H, Sadeghi B, et al. Intravitreal bevacizumab vs. sham treatment in acute branch retinal vein occlusion with macular edema: results at 3 months (report 1). *Graefes Arch Clin Exp Ophthalmol*. 2011;249:193–200.
17. Jaffe GJ, Schmitz-Valckenberg S, Boyer D, et al. Randomized trial to evaluate tandospirone in geographic atrophy secondary to age-related macular degeneration: the GATE study. *Am J Ophthalmol*. 2015;160:1226–1234.
18. Alm A, Grunden JW, Kwok KK. Five-year, multicenter safety study of fixed-combination latanoprost/timolol (Xalacom) for open-angle glaucoma and ocular hypertension. *J Glaucoma*. 2011;20:215–222.
19. Lee JW, Devanarayan V, Barrett YC, et al. Fit-for-purpose method development and validation for successful biomarker measurement. *Pharm Res*. 2006;23:312–328.
20. Danis RP. The clinical site-reading center partnership in clinical trials. *Am J Ophthalmol*. 2009;148:815–817.
21. Weintraub WS, Lüscher TF, Pocock S. The perils of surrogate endpoints. *Eur Heart J*. 2015;36:2212–2218.
22. Razzouk L, Farkouh ME. Imaging outcomes in cardiovascular clinical trials. *Nat Rev Cardiol*. 2009;6:524–531.
23. Ioannidis JP. Why most published research findings are false. *PLoS Med*. 2005;2:e124.
24. Fujimoto J, Swanson E. The development, commercialization, and impact of optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2016;57:OCT1–OCT13.
25. Rosenfeld PJ. Optical coherence tomography and the development of antiangiogenic therapies in neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2016;57:OCT14–OCT26.
26. Turner L, Shamseer L, Altman DG, et al. Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. *Cochrane Database Syst Rev*. 2012;11:MR000030.
27. Yao AC, Khajuria A, Camm CF, Edison E, Agha R. The reporting quality of parallel randomised controlled trials in ophthalmic surgery in 2011: a systematic review. *Eye (Lond)*. 2014;28:1341–1349.
28. Lai TY, Wong VW, Lam RF, Cheng AC, Lam DS, Leung GM. Quality of reporting of key methodological items of randomized controlled trials in clinical ophthalmic journals. *Ophthalmic Epidemiol*. 2007;14:390–398.
29. Farwell MD, Clark AS, Mankoff DA. How imaging biomarkers can inform clinical trials and clinical practice in the era of targeted cancer therapy. *JAMA Oncol*. 2015;1:421–422.

Investigative Ophthalmology & Visual Science