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Central Serous Chorioretinopathy: Long-Term Results After Photodynamic Therapy

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Central Serous Chorioretinopathy: Long-Term Results After Photodynamic Therapy

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THESIS OUTLINE

This Master thesis in Medicine consists of an Original Scientific Article, written between March 2021 and November 2021, with bibliographic research until September 2021.

This article was written with the goal of submission to the journal Oftalmologia. The Oftalmologia follows AMA Manual of Style (10th Edition) and the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Therefore, these instructions were followed and are presented in Appendix 1.

RESUMO

Introdução

A Coriorretinopatia Serosa Central (CSC) é uma síndrome idiopática caracterizada por descolamentos serosos, idiopáticos, da retina neurossensorial na região macular, secundários ao aumento da permeabilidade e derrame dos vasos coroideus. Embora os mecanismos fisiopatológicos subjacentes não estejam, ainda, totalmente compreendidos, a imagiologia multimodal auxiliou a compreensão da importância do epitélio pigmentar da retina (EPR) e da coroide no desenvolvimento da CSC. Na maioria dos casos, a CSC aguda é autolimitada e apresenta bom prognóstico. No entanto, quando não há resolução da CSC aguda após 3 meses, ou em casos de CSC crónica, deve ser considerado tratamento. A CSC crónica é definida pela presença de descolamento seroso da retina persistente, ou recorrência do descolamento foveal, por um longo período de tempo. Está, geralmente, associada a alterações atróficas e degenerativas da retina e do EPR, causando uma diminuição progressiva da acuidade visual. A terapia fotodinâmica (TFD) com verteporfina, guiada por ICGA, tem-se revelado eficaz na preservação da acuidade visual, bem como da função anatómica, uma vez que reduz a hiperpermeabilidade vascular coroideia. São poucos os estudos sobre a eficácia e segurança a longo prazo da TFD na CSC, e estão, na sua maioria, limitados a 5 anos. O objetivo do nosso estudo foi avaliar a eficácia e segurança da TFD *standard* com verteporfina, durante um período de seguimento mínimo de 13 anos, em doentes com CSC crónica, bem como explorar as alterações microestruturais e vasculares a longo prazo, relacionadas com a doença e com o tratamento.

Materiais e Métodos

Foi realizada uma análise retrospetiva de casos de CSC crónica da consulta de Retina Médica do CHUC. Foram incluídos 18 doentes com CSC crónica, tratados com TFD *standard*, e com, pelo menos, 13 anos de seguimento. As avaliações periódicas foram realizadas a cada 3 meses no primeiro ano, a cada 6 meses no segundo ano e, a partir daí, anualmente. Na visita final, todos os participantes foram submetidos a um exame oftalmológico completo, incluindo avaliação da melhor acuidade visual corrigida (MAVC), na escala ETDRS, exame de lâmpada de fenda, medição de pressão intraocular, e exame de fundo do olho sob midríase farmacológica. A imagiologia da retina e da coroide foi obtida recorrendo a abordagem multimodal com SD-OCT, SS-OCT, Optomap e OCTA. Os seguintes foram critérios de inclusão: 1) CSC crónica diagnosticada por angiografia fluoresceínica (AF) e confirmada por ICGA e OCT; 2) idade ≥ 18 anos; 3) CSC persistente há mais de 6 meses, ou alterações do EPR

induzidas por descolamentos multifocais recorrentes, associados a sintomas de CSC crónica com duração ≥ 6 meses; 4) capacidade de fornecer consentimento informado. Este estudo seguiu os princípios da Declaração de Helsínquia para pesquisa biomédica e foi aprovado pelo Comité de Ética local. Foi obtido consentimento informado de todos os participantes.

Resultados e Discussão

A nossa amostra é constituída por 23 olhos de 18 doentes, 15 homens (83.3%) e 3 mulheres (16.7%), com uma idade média de 63.9 ± 8.5 anos. O período médio de seguimento foi 15.8 ± 1.4 anos (intervalo, 13-18 anos). O número médio de tratamentos foi 1.2 ± 0.4, sendo o *spot* foveal localizado na região subfoveal em 36.8%, justafoveal em 36.8%, extrafoveal em 21.1%, e peripapilar em 5.3%. No início do estudo, estava presente fluído subretiniano (FSR) em todos os olhos, proliferação do EPR em 9.1%, e atrofia em 9.1%. A MAVC média inicial foi de 62.7 ± 22.7 letras (intervalo, 10-85 letras). Na última visita, a MAVC foi de 64.6 ± 19.2 letras (intervalo, 20-85 letras). Não houve uma melhoria estatisticamente significativa na MAVC ($P > 0.05$, Teste-T para amostras emparelhadas), embora tenha sido registado um ganho médio de 1.87 ± 11.9 letras (intervalo, -25 a 25 letras). No final do seguimento, apenas 3 olhos (13.04%) apresentavam FSR, 3 (13.04%) tinham fibrose e 15 (65.2%) apresentavam atrofia na visita final. A espessura macular central (EMC) média, definida como a espessura média no diâmetro central de 1 mm da grelha ETDRS, reduziu de 340.7 ± 114.9 µm na *baseline* para 228.7 ± 38.6 µm no final do seguimento ($P < 0.05$). O tamanho médio do *spot* da TFD foi 3.390 µm. Dezanove olhos (82.6%) foram submetidos a uma sessão única de TFD, e os outros 4 (17.4%) realizaram 2 sessões. Não houve casos de neovascularização coroideia (NVC) detetados na visita final.

Conclusão

Concluindo, este estudo constitui, tanto quanto é do nosso conhecimento, a investigação mais longa (superior a 13 anos) da eficácia e segurança da TFD *standard* na CSC crónica, até à data. O nosso estudo demonstrou que a TFD *standard* guiada por ICGA é um procedimento seguro, sem efeitos adversos graves, a nível ocular ou sistémico. Apenas 17.4% dos casos necessitaram de duas sessões, e não houve qualquer caso de progressão para neovascularização coroideia. No entanto, cerca de dois terços dos casos apresentava atrofia retiniana na visita final. Estudos randomizados, prospetivos e multicêntricos, com amostras amplas são necessários para determinar o regime ideal de TFD.

Palavras-chave: coriorretinopatia serosa central crónica, terapia fotodinâmica, fluído subretiniano, atrofia da retina, angiografia por tomografia de coerência ótica

ABBREVIATIONS

BCVA: best-corrected visual acuity

CSC: central serous chorioretinopathy

cCSC: chronic central serous chorioretinopathy

CMT: central macular thickness

CNV: choroidal neovascularization

DCP: deep capillary plexus

EDI: enhanced-depth imaging

FA: fluorescein angiography

FAF: fundus autofluorescence

ICGA: indocyanine green angiography

NRT: neuroretinal thickness

OCT: optical coherence tomography

OCTA: optical coherence tomography angiography

PDT: photodynamic therapy

RPE: retinal pigment epithelium

SCP: superficial capillary plexus

SRF: subretinal fluid

SS-OCT: Swept-Source optical coherence thickness

ABSTRACT

Introduction

Central Serous Chorioretinopathy (CSC) is an idiopathic syndrome characterized by idiopathic serous detachments of neurosensory retina at the macula, secondary to increased permeability and leakage from choroidal vessels. Although the underlying pathophysiological mechanisms are not fully understood, multimodal imaging shed new light into the choroidal and Retinal Pigment Epithelium (RPE) contribution to its pathogenesis. In most patients, acute CSC usually resolves without treatment and has a good prognosis. However, if there is no resolution of acute CSC after 3 months, or in case of chronic CSC, treatment should be considered. Chronic CSC is defined by the presence of a persistent serous retinal detachment or recurrence of foveal detachment for a long period of time, and it's often associated with atrophic and degenerative changes of the retina and RPE, leading to progressive visual acuity loss. ICGA-guided verteporfin photodynamic therapy (PDT) has been shown to be effective in preserving visual acuity as well as anatomical function, by reducing choroidal vascular hypermeability. There are few long-term studies on the efficacy and safety of PDT in CSC, and they are mostly limited to 5-years follow-ups. The aim of this report is to evaluate the 13-year follow-up of chronic CSC patients treated with standard-fluence PDT and to explore the long-term microstructural and vascular choroidal changes related to the disease and treatment.

Methods

A retrospective, interventional case-series analysis with a cross-sectional evaluation was conducted on 18 patients with cCSC, treated with standard PDT, and with at least 13 years of follow-up in Coimbra's University Hospital Center. Evaluations were performed every 3 months in the first year, every 6 months during the second year, and annually thereafter. All participants underwent a comprehensive ophthalmic examination, including best-corrected visual acuity (BCVA), measured with ETDRS charts, slit-lamp exam, intraocular pressure measurement and dilated fundus examination with a noncontact lens. Retinal and choroidal imaging was performed with SD-OCT, SS-OCT, Optomap and OCTA. The following were inclusion criteria: 1) chronic CSC diagnosed with fluorescein angiography (FA) and confirmed by ICGA and OCT; 2) age ≥ 18 years; 3) persistent CSC of >6-month duration or RPE changes induced by multifocal recurrent detachment associated with symptoms of cCSC lasting at least 6 months; 4) the provision of written informed consent. This study followed the tenets of the declaration of Helsinki for biomedical research and was approved by the local Ethic Committee. Informed consent was obtained.

Results and Discussion

A total of 23 eyes of 18 patients, 15 men (83.3%) and 3 women (16.7%), were included, with a mean age of 63.9 ± 8.5 years. The mean follow-up period was 15.8 ± 1.4 years (range, 13-18 years). The mean number of treatments was 1.2 ± 0.4, and the foveal spot was subfoveal in 36.8%, juxtafoveal in 36.8%, extrafoveal in 21.1% and peripapillary in 5.3%. Subretinal fluid was found in all eyes, RPE proliferation in 9.1% and atrophy in 9.1% of the eyes at baseline. The Initial mean BCVA was 62.7 ± 22.7 letters (range, 10-85 letters). In the last visit, BVCA was 64.6 ± 19.2 letters (range, 20-85 letters). There was not a statistically significant improvement in BCVA ($P > 0.05$, Paired-Samples T-Test), although a mean gain of 1.87 ± 11.9 letters (range, -25 to 25 letters) was registered. At the end of our follow-up, only 3 eyes (13.04%) presented subretinal fluid, 3 (13.04%) had fibrosis and 15 (65.2%) showed atrophy at the final visit. Mean central macular thickness (CMT), defined as the average thickness of the central 1 mm diameter of the ETDRS grid, reduced from 340.7 ± 114.9 µm at baseline to 228.7 ± 38.6 µm at the end of the follow-up ($P < 0.05$). The mean spot size was 3.390 µm. Nineteen eyes (82.6%) were submitted to only one session of PDT, and the other 4 (17.4%) underwent 2 sessions. There were no cases of choroidal neovascularization (CNV) detected in the final visit.

Conclusion

In conclusion, to the best of our knowledge, this study is the longest investigation (more than 13 years) of the efficacy and safety of standard PDT in cCSC to date. Our study showed that ICGA-guided PDT full-fluence is a safe procedure, with no ocular or systemic sever adverse effects. Only 17.4% of cases needed two sessions, and there was no case of progression to choroidal neovascularization. However, about two-thirds of the cases presented atrophy in the last visit. Furthermore, randomized, prospective multicenter studies with large samples are desirable to determine the optimal regime of PDT.

Key words: chronic central serous chorioretinopathy, photodynamic therapy, subretinal fluid, retinal atrophy, optical coherence tomography angiography

INTRODUCTION

Central Serous Chorioretinopathy (CSC) is a chorioretinal disease characterized by idiopathic serous neurosensory retinal detachments at the posterior pole of the fundus (1-8). CSC commonly affects young-to-middle-aged men (6, 9, 10). and although the exact cause of CSC is unclear, its pathogenesis is thought to be related to abnormalities of the retinal pigment epithelium (RPE) and/or choroid (1, 10-12). Risk factors include the use of corticosteroids, psychological stress, type A personality, among others. Despite the cause, the final pathway seems to be related to choroidal vascular hyperpermeability, resulting in leakage and accumulation of subretinal fluid (SRF) (1, 3-5, 7, 9-11).

Indocyanine green angiography (ICGA) characteristically shows multifocal areas of choroidal abnormalities, such as vascular filling delay, congested and dilated choroidal vessels, choroidal staining, and hyperfluorescent areas in late frames of the angiogram (1, 2, 4, 5, 8-11). Optical coherence tomography angiography (OCTA) is a noninvasive method that allows a direct insight into choriocapillaris perfusion and vasculature patterns, without the need for a dye injection (4, 5, 8). Previous studies using OCTA among CSC patients have reported irregular flow patterns, involving choriocapillaris dilatation with increasing flow signals, and focal or defused dark areas with flow signal voids, corresponding to the ICGA abnormalities (4, 5). Other studies using enhanced-depth imaging (EDI) optical coherence tomography (OCT) or Swept-Source OCT (SS-OCT) have shown a thickened choroid and/or dilated choroidal vessels in patients with CSC, which might indicate increased hydrostatic pressure (7, 8, 13).

CSC is subcategorized in 2 categories: acute CSC and chronic CSC (cCSC). Acute CSC usually is self-limiting and has a good prognosis, with normal vision returning within 3 or 4 months in the majority of cases (1, 3, 4, 6, 7, 10). However, the recurrence rate is up to 50% without any treatments and 10% of patients have more than 3 recurrences when the follow-up lasts for 15 years (6, 8). In cases with persistent SRF and more extensive retinal and choroidal damage, characteristic of cCSC, significant central visual impairment or permanent symptoms and changes of the outer segments of the photoreceptors and retinal pigment epithelium (RPE) may occur (1-4, 6-9).

Treatment should be considered after 3 months without resolution of acute CSC and in chronic CSC (1). ICGA-guided photodynamic therapy (PDT) has been shown to be an effective angiomodulator treatment of cCSC (1-5, 7, 9, 10, 12). The primary target of treatment is the inner choroid, leading to a short-term narrowing of choroidal vessels and long-term vascular remodeling, thus reducing extravascular leakage (1-5, 9, 10,

12, 14).

Many studies have been published since the first report produced by Yannuzzi *et al* (15) in 2003, and numerous protocols have been tested: standard-fluence PDT, half-dose PDT, half-fluency PDT, and half-time PDT (1, 9, 11). Possible complications of conventional PDT are: RPE and neuroretinal atrophy, choroidal ischemia, and secondary choroidal neovascularization (CNV) (3, 5, 7, 10, 12, 16).

PDT causes a far less destructive effect on the RPE compared to other treatment methods introduced in the past, such as focal laser photocoagulation (14). It can result in visual improvement, shortened duration of symptoms and reduced recurrence rates, with a good safety profile (16). Long-term studies, up to 4 years and 6 months, showed noteworthy improvements in visual and anatomic outcomes with low recurrence rates with full-fluence PDT for cCSC (1, 7, 17). Another study conducted by Rouvas *et al.* (18) demonstrated that the application of standard PDT is efficient, providing anatomic and functional improvement in the treated eyes, with a low recurrence rate of 13.4% after a mean follow-up period of 35.8 ±16.6 months. In the last-mentioned study, none of the patients presented adverse effects, reinforcing the efficacy and safety of the proposed method.

Modifications of PDT parameters have been attempted and have shown similar efficacy to standard PDT in terms of anatomical and visual outcomes, and usually with fewer complications (5, 7). Nevertheless, there are limited studies with large sample size and long-term follow-up to provide evidence regarding the long-term efficacy and safety of PDT in cCSC, especially full-fluence PDT (1, 2, 7, 9, 17). Furthermore, studies on the long-term choroidal vascular effects of PDT by non-invasive methodologies such as SS-OCT and OCTA are few in the literature.

The aim of this report is to evaluate the 13-year follow-up of chronic CSC patients treated with standard-fluence PDT and to explore the long-term microstructural and vascular retinal and choroidal changes related to the disease and treatment. To the best of our knowledge, this is the longest follow-up ever studied for the treatment of cCSC with PDT.

MATERIALS AND METHODS

A retrospective, interventional case-series analysis with a cross-sectional evaluation was conducted on 18 patients with cCSC, treated with standard PDT, and with at least 13 years of follow-up in Coimbra's University Hospital Center. This study followed the tenets of the Declaration of Helsinki, and the approval of the Institution Review Board was obtained.

The inclusion criteria were: 1) chronic CSC diagnosed with fluorescein angiography (FA) and confirmed by ICGA and OCT; 2) patient's age 18 years or older; 3) persistent CSC of >6-month duration or RPE changes induced by multifocal recurrent detachment associated with symptoms of cCSC lasting at least 6 months; 4) the provision of written informed consent. The following were exclusion criteria: 1) the presence of any other macular conditions that might compromise visual acuity; and 2) hepatic insufficiency, known hypersensitivity to fluorescein, or any other condition that might contraindicate PDT or angiographic examinations.

The presence of diffuse or poorly defined widespread areas of leakage in FA, originating from broad areas of RPE damage, made the diagnosis of cCSC. ICGA was performed to verify the presence of choroidal vascular hyperpermeability, to calculate its size, and to guide the PDT if indicated. Baseline evaluation involved best-corrected visual acuity (BCVA) with Early Treatment Diabetic Retinopathy Study chart, fundus eye examination, FA (Topcon TRC-50 IA; Topcon, Tokyo, Japan), ICG-A (Topcon TRC 50-IA; Topcon), and OCT (OCT Stratus 3; Carl Zeiss Meditec, Dublin, CA). The OCT was intended for monitoring and measuring the SRF, for evaluating structural changes of the neurosensory retina and RPE and the presence of intraretinal cysts, and to measure the central macular thickness (CMT). CMT was defined as the average thickness of the central 1 mm diameter of the ETDRS grid. During all follow-up, NRT and SRF height were manually measured in Stratus 3 OCT. To calculate NRT, markers were positioned on the fovea centralis, between the internal limiting membrane and the anterior limit of the subretinal fluid. To determine the SRF thickness, markers were placed between the anterior limit of the SRF and the RPE, without including it. The sum of the neural retina thickness and the subretinal fluid thickness corresponds to total CMT. Baseline retinal atrophy was reevaluated in OCT and redefined as complete RPE and outer retinal atrophy (cRORA) (19).

All patients were treated with standard PDT with verteporfin, according to the recommended protocol for CNV secondary to Age-Related Macular Degeneration (Treatment of Age-Related Macular Degeneration (TAP) Study Group 1999). Every

patient was administered with 6 mg/m^2 of intravenous verteporfin over 10 minutes, which was then activated by a laser wavelength of 698 nm, 15 minutes after the infusion started. It used an energy intensity of 600 mW/cm^2 for 83 seconds, similar to a total dose of energy of 50J/cm^2. Standard PDT was applied only to areas of choroidal hyperpermeability (plus 1 mm diameter) identified in ICGA, including the subfoveal area. Individual spots were performed sequentially in multiple leaks separated by >2 mm because they were >1 mm diameter. Bilateral treatments were performed in the same session. Retreatment was performed when patients presented clinical evidence of persistence or recurrence. Recurrence was based on OCT findings, such as subretinal or intraretinal fluid, and was then confirmed with FA and ICGA.

Evaluations were performed every 3 months in the first year, every 6 months during the second year, and annually thereafter.

BCVA was considered improved when there was a gain of five or more letters, and vision loss when there was a decrease of at least five letters in relation to the initial visit BCVA. At each visit, besides the evaluation of BCVA and the measurement of SRF thickness and NRT, the assessment also included the number of treatments, the presence of side effects, the presence of recurrences.

All 18 patients were convoked for a last visit, in which Spectralis SD-OCT and SS-OCT (Topcon DRI OCT-1 Atlantis) were performed to measure the SRF, for evaluating structural changes of the neurosensory retina, RPE and choroid, such as development of RPE atrophy (cRORA) and/or fibrosis, and to measure the central macular thickness (CMT) and the choroidal thickness. SS-OCT and OCTA were performed in treated and non-treated contralateral eyes, in order to compare choriocapillaris' flow densities, superficial capillary plexus (SCP) and deep capillary plexus (DCP) vessel densities, and confirm the presence of signs of conversion to neovascular disease in study eyes. Fundus autofluorescence (FAF) was performed for identification of hyperfluorescent or hypofluorescent areas, descending tracts and the status of the fovea.

Statistical analyses were performed using STATA software (version 16.0). Descriptive statistics, confirmation of normality with the Kolmogorov-Smirnov test, inferential statistics using paired t-tests and uni and multivariate linear regressions were performed. For all statistical tests, a p value < 0.05 was considered statistically significant.

RESULTS

Twenty-three eyes of 18 patients were included in the study, 15 men (83.3%) and 3 women (16.7%). The patients had a mean age of 63.9 ± 8.5 years, with a minimum of 48 and a maximum of 81 years. Mean duration of cCSC, defined as the interval between baseline visit and treatment, was 8.5 months. All patients were followed for a mean period of 15.8 ± 1.4 years (range, 13-18 years). The mean PDT spot size was 3.390 µm. Five of the patients had bilateral CSC. Nineteen eyes (82.6%) were submitted to only one session of PDT, and the other 4 (17.4%) underwent 2 sessions. The mean number of treatments was 1.2 ± 0.4, and the foveal spot was subfoveal in 36.8%, juxtafoveal in 36.8%, extrafoveal in 21.1% and peripapillary in 5.3%. Of the 4 eyes which underwent a second session of PDT, 2 were retreated after 6 months because of the presence of subretinal fluid and cystic changes in OCT, 1 after 21 months because of recurrence of subretinal fluid, and 1 after 6 years. No systemic or ocular side effects were found to be related to the treatment.

BCVA Evolution

The initial mean BCVA was 62.7 ± 22.7 letters (range, 10-85 letters), it was 67.1 ± 22.4 letters (range, 10-90 letters) after the first year of follow-up and, in the last visit, it was 64.6 ± 19.2 letters (range, 30-85 letters). There was a statistically significant improvement ($P < 0.05$) in BCVA at the first year of follow-up, with a mean gain of 5.08 ± 10.36 letters. This gain was, however, lost at the end of follow-up, despite a final mean gain of 1.87 ± 11.9 letters ($p>0.05$). The progression of BCVA over the years is represented in figure 1.

Visual acuity at the end of our follow-up improved in 8 eyes (34.8%), remained unchanged in 9 eyes (39.1%), and decreased in 6 eyes (26.1%). Differences in visual acuity were not correlated with the spot nor with the number of PDT sessions.

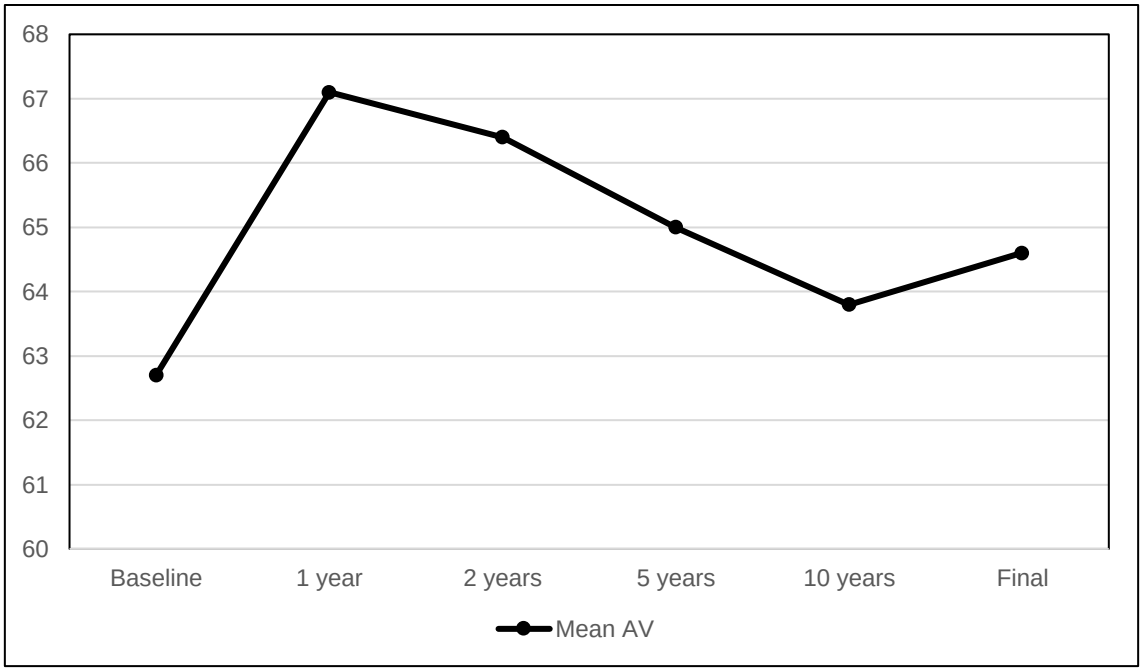

Fig. 1. Progression of BCVA over the years (15.8 ± 1.4 years), using ETDRS Scoring Method.

CMT Evolution

Mean CMT decreased from 340.7 ± 114.9 µm at baseline to 290 ± 152.8 µm after the first year of follow-up. It was 228.7 ± 38.6 µm at the end of the follow-up. There was both a statistically significant decrease ($P < 0.05$) in this measure, when comparing baseline to one-year follow-up, and to the final (figure 2).

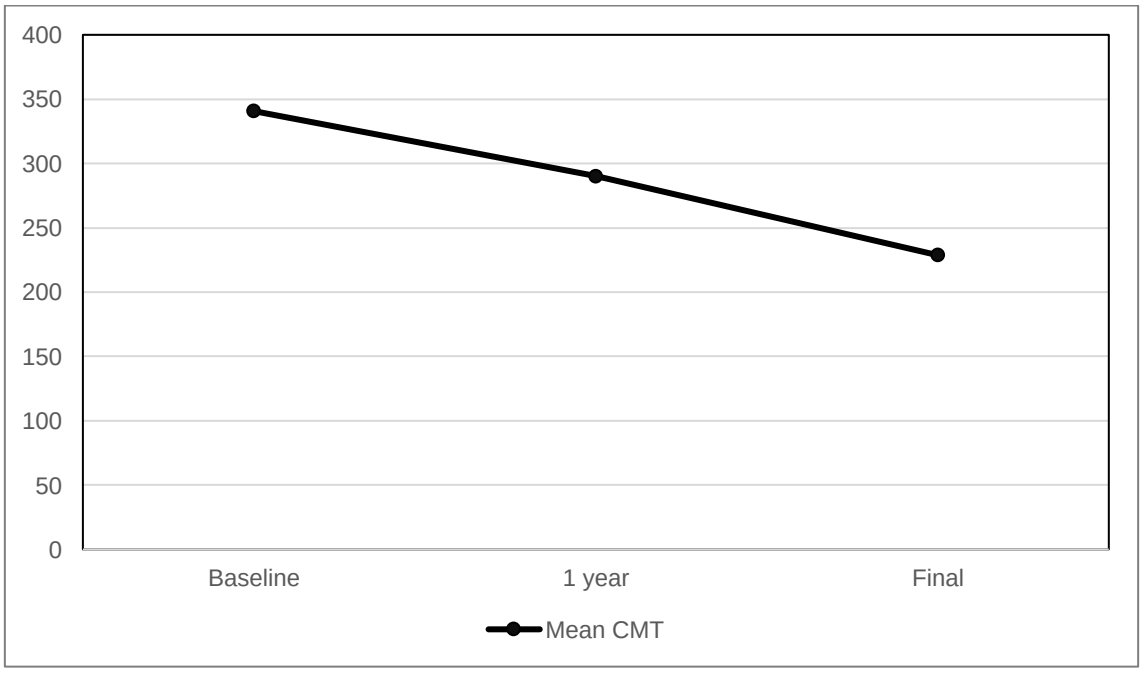

Fig. 2. Progression of CMT over the years (15.8 ± 1.4 years), evaluated by OCT.

Morphologic Results

The morphologic results were evaluated by OCT. Subretinal fluid was found in all eyes, RPE proliferation in 9.1% and atrophy in 9.1% of the eyes at baseline. At the end of our follow-up, only 3 eyes (13.04%) presented subretinal fluid, 3 (13.04%) had fibrosis and 15 (65.2%) showed some degree of atrophy at the final visit. The 3 eyes who presented SRF in the last OCT had a final BCVA of 85, 45 and 35 letters. The first 2 underwent only one session of PDT, and the latter 2 sessions. Mean BCVA of the eyes which presented atrophy in the last visit was 60.7 ± 21.3 letters, and in the eyes without atrophy in the last visit, it was 71.9 ± 12.5. However, this difference was not statistically significant. When comparing the presence of atrophy in the last visit OCT with the number of treatments, the foveal spot and baseline CMT, we found there was no statistically significant relation between these variables ($P > 0.05$). However, out of the eyes in which PDT spot involved the fovea (36.8%), 57.1% presented atrophy in the OCT at the final visit, while only 14.3% showed atrophy at baseline. This difference was not statistically significant.

In the final visit, the FAF showed that 12 eyes (57.1%) had hyperfluorescent areas, which represent cellular suffering, 17 eyes (80.9%) showed hypofluorescent areas, which represent cellular death, 4 eyes (19.1%) presented descending tracts, and 17 eyes (80.9%) exhibited alterations affecting the fovea (both hyper and hypo-autofluorescent changes).

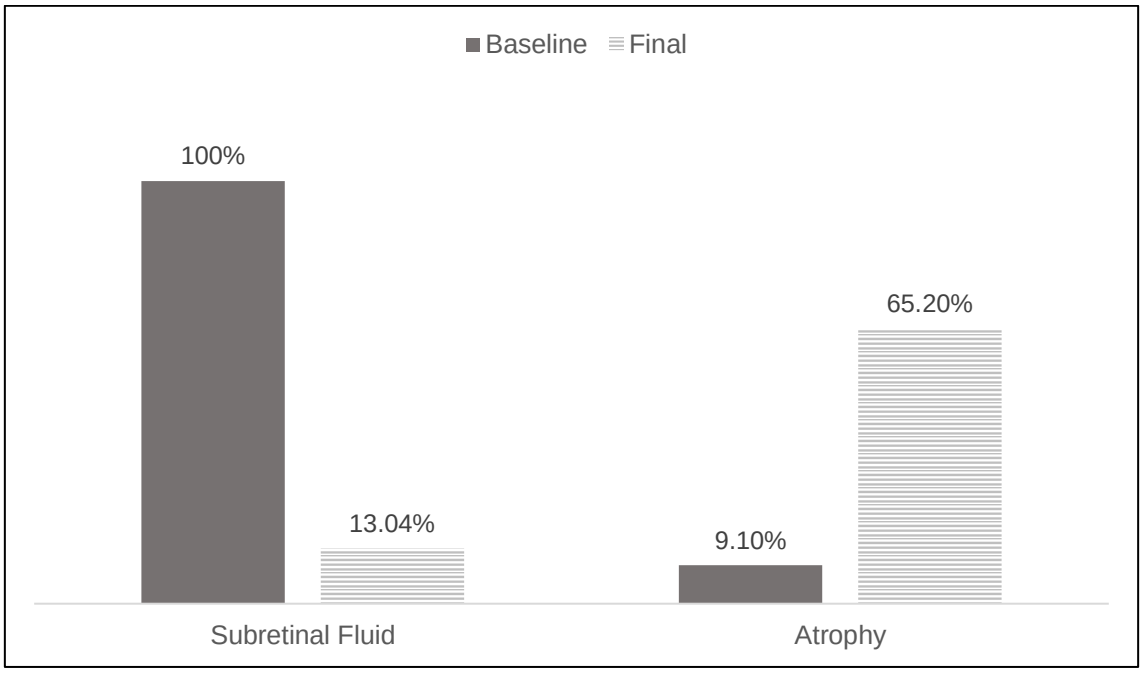

Fig. 3. Comparison of retinal morphologic changes, assessed by OCT, between baseline and the end of the follow-up.

Choroidal's Structural Long-Term Changes

The final mean subfoveal choroidal thickness of treated eyes was 262.4 ± 87.86 µm. As for the untreated contralateral eyes, this value was 234.3 ± 24.5 µm. No significant differences between treated and non-treated eyes were found (P > 0.05), despite CSC treated eyes having in average a thicker choroid.

The OCTA was used to compare the choriocapillaris' flow density and SCP and DCP vessel densities, in both treated and non-treated contralateral eyes. We found there was no statistically significant difference (P > 0.05) between each of these measurements, when comparing treated eyes with non-treated contralateral eyes (table 2). BCVA at the end of our follow-up was not associated with the choriocapillaris' flow density, nor with SCP and DCP vessel densities of treated eyes (P > 0.05). There were also no cases of CNV, nor other signs related to progression to neovascular disease found in OCTA in the final visit.

	Choriocapillaris' flow density	**SCP vessel density**	**DCP vessel density**
Treated	199.9 ± 630.1	48.5 ± 4.8	45.9 ± 3.8
Non-treated	239.7 ± 731.6	47.7 ± 4.6	46.8 ± 5.1

Table 1. Comparison between treated and non-treated eyes with PDT regarding capillary plexus density and the flow density of the choriocapillaris.

DISCUSSION

In the current report, we analyze the long-term results of treatment with standard PDT with verteporfin in cCSC, and we also explore the associated structural and vascular choroidal changes. We found that visual acuity outcome was not associated with the foveal spot location nor with the number of PDT sessions, although the pattern of visual improvement can be influenced by the progression of atrophic changes associated with the disease. Only 17.4% of cases needed two sessions, and there was no case of progression to choroidal neovascularization. However, about two-thirds of the cases presented atrophy in the last visit.

CSC is not a completely benign disease, as RPE atrophy and the associated visual loss seen in chronic and persistent CSC is a slow but continuous process (20-22). Different treatments have been previously proposed in managing cases of chronic or persistent CSC, and even though some might offer a more rapid resolution of SRF as, for example, focal laser at the RPE layer, these treatments did not affect the final functional outcomes and the recurrence rate of the disease (20). PDT is generally recommended for cCSC, and recent theories lead us to believe its mechanism of action is related to the release of free radicals that damage endothelium, reducing choroidal vasculature hyperpermeability and extravascular leakage, and provoking long-term vascular remodeling (12, 23-25). However, there is a lack of studies on the long-term effects of PDT in cCSC. Our report is the first to describe the efficacy, safety and the chorioretinal changes 13 or more years after standard PDT for cCSC.

If left untreated, cCSC can lead to irreversible changes in the neurosensory retina, progressive damage of RPE, and consequential worse visual prognosis (1, 26). Currently, there are no standard therapeutic protocols for cCSC. Although, many other studies have shown that ICGA-guided verteporfin PDT with a standard protocol could be effective in chronic CSC, with both visual and anatomical improvement reducing the SRF. Photodynamic therapy enables constriction of inner choriocapillaris vessels followed by long-term vascular remodeling and also choriocapillaris hypoperfusion (20, 27, 28).

Vasconcelos *et al.* (12) reported that 5 years after standard PDT, all 17 eyes of the 15 patients included in their study had complete resolution of SRF, with a significant improvement in mean BCVA and reduction in choroidal thickness. In our report, visual acuity improved in 34.8%, and decreased in 26.1%. After one year of treatment, gain in visual acuity was significant, however this was lost at the end of follow-up, with a final mean gain of only 1.87 ± 11.9 letters.The average number of treatments was 1.2 ± 0.4.

Furthermore, 82.6% of eyes were submitted to one session of PDT, while 17.4% (4 eyes) underwent 2 sessions, either because of persistence of SRF, or because of presence of SRF and cystic changes in OCT. Differences in visual acuity outcome were not associated with the foveal spot location nor with the number of PDT sessions each eye underwent. Three eyes presented SRF in the last OCT. The first 2 underwent only one session of PDT, and the latter 2 sessions. Another study by Silva *et al*. (1) found that 93.4% eyes had SRF resolution and the mean BCVA improved significantly from 58.8 letters to 66.9 letters at the end of a 4-year follow-up period. The anatomical success rate in our study was comparable to these studies. However, our pattern of visual improvement was different from observed in latter studies. This could be due to longer follow-up with progression of atrophic changes. Retinal pigment epithelium atrophy, chorioretinal scars, and choroidal hypoperfusion, all of which can cause outer retinal layer attenuation, have been assigned to standard PDT (1). At the end of our ≥ 13-years follow-up, resolution of subretinal fluid occurred in 87% of cases, 13% had fibrosis and 65% showed atrophy at the final visit. Furthermore, out of the eyes which PDT spot involved the fovea (46.8%), 57.1% presented atrophy in the OCT at the final visit, while only 14.3% were showing atrophy at baseline. However, the number of treatments, the foveal spot location and baseline CMT had no statistically significant relation to atrophy in the last visit. Therefore, despite being difficult to draw definite conclusions regarding the impact of PDT in atrophy development, and therefore in final BCVA, this long-term finding could be due only to the chronicity of the disease and its preferential location in the central macula, and not to treatment itself.

No systemic or ocular side effects were found to be related to the treatment. Piccolino *et al.* (29) noted a 12.5% retreatment rate in 9 months of follow-up. A study by Tarantola *et al.* (30), with an average follow-up of 21.9 months, established that 27.3% (3 of 11 eyes) required 2 treatment sessions because of reappearance of subretinal fluid. Our rate of treatment is similar to other series with shorter follow-up.

OCTA was performed in both untreated and PDT-treated eyes to assess the density of the capillary plexus vasculature and the flow density of the choriocapillaris layer. No significant differences between treated and non-treated eyes were found, despite CSC treated eyes having in average a thicker choroid. Other studies using OCT or SS-OCT have shown a thickened choroid and/or dilated choroidal vessels in patients with CSC, which might indicate increased hydrostatic pressure in the choroid (7, 8, 13). These leads us to conclude these changes are associated with the disease itself, rather than with PDT. Interestingly, untreated eyes showed a higher mean vascular density of the choriocapillaris compared to treated eyes (239.7 µm vs. 199.9 µm). This might be

explained by the remodeling of the choriocapillaris vasculature resulting from the treatment or the natural progression of the disease, in which compression by dilated choroidal vessels causes progressive atrophy of the choriocapillaris, or from both.

No cases of CNV nor other signs related to progression to neovascular disease were found in treated eyes. Therefore, neovascularization does not appear to be related to PDT, nor does any ischemia induced in the choroid seem to be caused by this treatment. In the same study previously mentioned, Vasconcelos *et al.* (12) observed that morphological and functional chorioretinal changes were not correlated with the location of the treatment, neither with the progression of visual acuity, and are more likely to be related to the disease itself than with the treatment provided. In our report, no systemic adverse effects were noticed as well, which confirms previous results showing PDT with verteporfin as a safe method in the treatment of cCSC. However, there were some recurrences, and cases of RPE atrophy were observed in the OCT at the final visit, limiting visual gains in the long-term.

Our study has several limitations, including the retrospective design, the use of Stratus 3 OCT, not being able to follow-up the outer retinal layers alterations since baseline, the small sample size, and the fact that we did not compare the outcomes of full-fluence PDT and half-fluence PDT, which is now more commonly used in clinical practice. Additionally, the irregularity of the follow-up (every 3 months in the first year, every 6 months during the second year, and annually thereafter), especially due to cases of patients who would miss visits, may also be considered a limitation in this study, even so unscheduled visits were allowed in the presence of symptoms. Nevertheless, to the best of our knowledge, this is the longest follow-up (an average of 16 years) of treatment outcomes of full-fluence PDT in cCSC to date.

In conclusion, our results support the long-term effectiveness and safety of standard PDT with verteporfin, as a treatment for cCSC. These results are extremely relevant in the comprehension of the role of PDT in chronic CSC, considering this is a disease without any standard therapeutic protocols established. Furthermore, randomized, prospective multicenter studies with large samples on the long-term effects of PDT are necessary to determine the guidelines of this treatment, in order to prevent recurrences and ocular or systemic adverse effects.

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APPENDICES

Appendix 1

Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals

Updated December 2019

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I. About the Recommendations

A. Purpose of the Recommendations

ICMJE developed these recommendations to review best practice and ethical standards in the conduct and reporting of research and other material published in medical journals, and to help authors, editors, and others involved in peer review and biomedical publishing create and distribute accurate, clear, reproducible, unbiased medical journal articles. The recommendations may also provide useful insights into the medical editing and publishing process for the media, patients and their families, and general readers.

B. Who Should Use the Recommendations?

These recommendations are intended primarily for use by authors who might submit their work for publication to ICMJE member journals. Many non-ICMJE journals voluntarily use these recommendations (see www.icmje.org/journals-following-the-icmje-recommendations/). The ICMJE encourages that use but has no authority to monitor or enforce it. In all cases, authors should use these recommendations along with individual journals' instructions to authors. Authors should also consult guidelines for the re-

porting of specific study types (e.g., the CONSORT guidelines for the reporting of randomized trials); see www.equator-network.org.

Journals that follow these recommendations are encouraged to incorporate them into their instructions to authors and to make explicit in those instructions that they follow ICMJE recommendations. Journals that wish to be identified on the ICMJE website as following these recommendations should notify the ICMJE secretariat at www.icmje.org/journals-following-the-icmje-recommendations/journal-listing-request-form/. Journals that in the past have requested such identification but who no longer follow ICMJE recommendations should use the same means to request removal from this list.

The ICMJE encourages wide dissemination of these recommendations and reproduction of this document in its entirety for educational, not-for-profit purposes without regard for copyright, but all uses of the recommendations and document should direct readers to www.icmje.org for the official, most recent version, as the ICMJE updates the recommendations periodically when new issues arise.

C. History of the Recommendations

The ICMJE has produced multiple editions of this document, previously known as the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URMs). The URM was first published in 1978 as a way of standardizing manuscript format and preparation across journals. Over the years, issues in publishing that went well beyond manuscript preparation arose, resulting in the development of separate statements, up-dates to the document, and its renaming as "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" to reflect its broader scope. Previous versions of the document may be found in the "Archives" section of www.icmje.org.

II. Roles and Responsibilities of Authors, Contributors, Reviewers, Editors, Publishers, and Owners

A. Defining the Role of Authors and Contributors

1. Why Authorship Matters

Authorship confers credit and has important academic, social, and financial implications. Authorship also implies responsibility and accountability for published work. The following recommendations are intended to ensure that contributors who have made substantive intellectual contributions to a paper are given credit as authors, but also that contributors credited as authors understand their role in taking responsibility and being accountable for what is published.

Because authorship does not communicate what contributions qualified an individual to be an author, some journals now request and publish information about the contributions of each person named as having participated in a submitted study, at least for original research. Editors are strongly encouraged to develop and implement a contributorship policy. Such policies remove much of the ambiguity surrounding contributions, but leave unresolved the question of the quantity and quality of contribution that qualify an individual for authorship. The ICMJE has thus developed criteria for authorship that can be used by all journals, including those that distinguish authors from other contributors.

2. Who Is an Author?

The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged—see Section II.A.3 below. These authorship criteria are intended to reserve the status of authorship for those who deserve credit and can take responsibility for the work. The criteria are not intended for use as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criterion #s 2 or 3. Therefore, all individuals who meet the first criterion should have the opportunity to participate in the review, drafting, and final approval of the manuscript.

The individuals who conduct the work are responsible for identifying who meets these criteria and ideally should do so when planning the work, making modifications as appropriate as the work progresses. We encourage collaboration and co-authorship with colleagues in the locations where the research is conducted. It is the collective responsibility of the authors, not the journal to which the work is submitted, to determine that all people named as authors meet all four criteria; it is not the role of journal editors to determine who qualifies or does not qualify for authorship or to arbitrate authorship conflicts. If agreement cannot be reached about who qualifies for authorship, the institution(s) where the work was performed, not the journal editor, should be asked to investigate. The criteria used to determine the order in which authors are listed on the byline may vary, and are to be decided collectively by the

author group and not by editors. If authors request removal or addition of an author after manuscript submission or publication, journal editors should seek an explanation and signed statement of agreement for the requested change from all listed authors and from the author to be removed or added.

The corresponding author is the one individual who takes primary responsibility for communication with the journal during the manuscript submission, peer review, and publication process. The corresponding author typically ensures that all the journal's administrative requirements, such as providing details of authorship, ethics committee approval, clinical trial registration documentation, and disclosures of relationships and activities, are properly completed and reported, although these duties may be delegated to one or more coauthors. The corresponding author should be available throughout the submission and peer-review process to respond to editorial queries in a timely way, and should be available after publication to respond to critiques of the work and cooperate with any requests from the journal for data or additional information should questions about the paper arise after publication. Although the corresponding author has primary responsibility for correspondence with the journal, the ICMJE recommends that editors send copies of all correspondence to all listed authors.

When a large multi-author group has conducted the work, the group ideally should decide who will be an author before the work is started and confirm who is an author before submitting the manuscript for publication. All members of the group named as authors should meet all four criteria for authorship, including approval of the final manuscript, and they should be able to take public responsibility for the work and should have full confidence in the accuracy and integrity of the work of other group authors. They will also be expected as individuals to complete disclosure forms.

Some large multi-author groups designate authorship by a group name, with or without the names of individuals. When submitting a manuscript authored by a group, the corresponding author should specify the group name if one exists, and clearly identify the group members who can take credit and responsibility for the work as authors. The byline of the article identifies who is directly responsible for the manuscript, and MEDLINE lists as authors whichever names appear on the byline. If the byline includes a group name, MEDLINE will list the names of individual group members who are authors or who are collaborators, sometimes called non-author contributors, if there is a note associated with the byline clearly stating that the individual names are elsewhere in the paper and whether those names are authors or collaborators.

3. Non-Author Contributors

Contributors who meet fewer than all 4 of the above criteria for authorship should not be listed as authors, but they should be acknowledged. Examples of activities that alone (without other contributions) do not qualify a contributor for authorship are acquisition of funding; general supervision of a research group or general administrative support; and writing assistance, technical editing, language editing, and proofreading. Those whose contributions do not justify authorship may be acknowledged individually or together as a group under a single heading (e.g., "Clinical Investigators" or "Participating Investigators"), and their contributions should be specified (e.g., "served as scientific advisors," "critically reviewed the study proposal," "collected data," "provided and cared for study patients", "participated in writing or technical editing of the manuscript").

Because acknowledgment may imply endorsement by acknowledged individuals of a study's data and conclusions, editors are advised to require that the corresponding author obtain written permission to be acknowledged from all acknowledged individuals.

B. Disclosure of Financial and Non-Financial Relationships and Activities, and Conflicts of Interest

Public trust in the scientific process and the credibility of published articles depend in part on how transparently an author's relationships and activities, directly or topically related to a work, are handled during the planning, implementation, writing, peer review, editing, and publication of scientific work.

The potential for conflict of interest and bias exists when professional judgment concerning a primary interest (such as patients' welfare or the validity of research) may be influenced by a secondary interest (such as financial gain). Perceptions of conflict of interest are as important as actual conflicts of interest.

Individuals may disagree on whether an author's relationships or activities represent conflicts. Although the presence of a relationship or activity does not always indicate a problematic influence on a paper's content, perceptions of conflict may erode trust in science as much as actual conflicts of interest. Ultimately, readers must be able to make their own judgments regarding whether an author's relationships and activities are pertinent to a paper's content. These judgments require transparent disclosures. An author's complete disclosure demonstrates a commitment to transparency and helps to maintain trust in the scientific process.

Financial relationships (such as employment, consultancies, stock ownership or options, honoraria, patents, and paid expert testimony) are the most easily identifiable, the ones most often judged to represent potential conflicts of interest and thus the most likely to undermine the credibility of the journal, the authors, and science itself. Other interests may also represent or be perceived as conflicts, such as personal relationships or rivalries, academic competition, and intellectual beliefs.

Authors should avoid entering in to agreements with study sponsors, both for-profit and nonprofit, that interfere

with authors' access to all of the study's data or that interfere with their ability to analyze and interpret the data and to prepare and publish manuscripts independently when and where they choose. Policies that dictate where authors may publish their work violate this principle of academic freedom. Authors may be required to provide the journal with the agreements in confidence.

Purposeful failure report those relationships or activities specified on the journal's disclosure form is a form of misconduct, as is discussed in Section III.B.

1. Participants

All participants in the peer-review and publication process—not only authors but also peer reviewers, editors, and editorial board members of journals—must consider and disclose their relationships and activities when fulfilling their roles in the process of article review and publication.

a. Authors

When authors submit a manuscript of any type or format they are responsible for disclosing all relationships and activities that might bias or be seen to bias their work. The ICMJE has developed a Disclosure Form to facilitate and standardize authors' disclosures. ICMJE member journals require that authors use this form, and ICMJE encourages other journals to adopt it.

b. Peer Reviewers

Reviewers should be asked at the time they are asked to critique a manuscript if they have relationships or activities that could complicate their review. Reviewers must disclose to editors any relationships or activities that could bias their opinions of the manuscript, and should recuse themselves from reviewing specific manuscripts if the potential for bias exists. Reviewers must not use knowledge of the work they're reviewing before its publication to further their own interests.

c. Editors and Journal Staff

Editors who make final decisions about manuscripts should recuse themselves from editorial decisions if they have relationships or activities that pose potential conflicts related to articles under consideration. Other editorial staff members who participate in editorial decisions must provide editors with a current description of their relationships and activities (as they might relate to editorial judgments) and recuse themselves from any decisions in which an interest that poses a potential conflict exists. Editorial staff must not use information gained through working with manuscripts for private gain. Editors should regularly publish their own disclosure statements and those of their journal staff. Guest editors should follow these same procedures.

Journals should take extra precautions and have a stated policy for evaluation of manuscripts submitted by individuals involved in editorial decisions. Further guidance is available from COPE (https://publicationethics.org/files/A_Short_Guide_to_Ethical_Editing.pdf) and WAME (http://wame.org/conflict-of-interest-in-peer-reviewed-medical-journals).

2. Reporting Relationships and Activities

Articles should be published with statements or supporting documents, such as the ICMJE Disclosure Form, declaring:

– Authors' relationships and activities; and

– Sources of support for the work, including sponsor names along with explanations of the role of those sources if any in study design; collection, analysis, and interpretation of data; writing of the report; any restrictions regarding the submission of the report for publication; or a statement declaring that the supporting source had no such involvement or restrictions regarding publication; and

– Whether the authors had access to the study data, with an explanation of the nature and extent of access, including whether access is ongoing.

To support the above statements, editors may request that authors of a study sponsored by a funder with a proprietary or financial interest in the outcome sign a statement, such as "I had full access to all of the data in this study and I take complete responsibility for the integrity of the data and the accuracy of the data analysis."

C. Responsibilities in the Submission and Peer-Review Process

1. Authors

Authors should abide by all principles of authorship and declaration of relationships and activities detailed in section IIA and B of this document.

a. Predatory or Pseudo-Journals

A growing number of entities are advertising themselves as "scholarly medical journals" yet do not function as such. These journals ("predatory"or "pseudo-journals") accept and publish almost all submissions and charge article processing (or publication) fees, often informing authors about this after a paper's acceptance for publication. They often claim to perform peer review but do not and may purposefully use names similar to well established journals. They may state that they are members of ICMJE but are not (see www.icmje.org for current members of the ICMJE) and that they follow the recommendations of organizations such as the ICMJE, COPE and WAME. Researchers must be aware of the existence of such entities and avoid submitting research to them for publication. Authors have a responsibility to evaluate the integrity, history, practices and reputation of the journals to which they submit manuscripts. Guidance from various organizations is available to help identify the characteristics of rep-

utable peer-reviewed journals (www.wame.org/identifying-predatory-or-pseudo-journals and www.wame.org/principles-of-transparency-and-best-practice-in-scholarly-publishing). Seeking the assistance of scientific mentors, senior colleagues and others with many years of scholarly publishing experience may also be helpful.

Authors should avoid citing articles in predatory or pseudo-journals.

2. Journals

a. Confidentiality

Manuscripts submitted to journals are privileged communications that are authors' private, confidential property, and authors may be harmed by premature disclosure of any or all of a manuscript's details.

Editors therefore must not share information about manuscripts, including whether they have been received and are under review, their content and status in the review process, criticism by reviewers, and their ultimate fate, to anyone other than the authors and reviewers. Requests from third parties to use manuscripts and reviews for legal proceedings should be politely refused, and editors should do their best not to provide such confidential material should it be subpoenaed.

Editors must also make clear that reviewers should keep manuscripts, associated material, and the information they contain strictly confidential. Reviewers and editorial staff members must not publicly discuss the authors' work, and reviewers must not appropriate authors' ideas before the manuscript is published. Reviewers must not retain the manuscript for their personal use and should destroy paper copies of manuscripts and delete electronic copies after submitting their reviews.

When a manuscript is rejected, it is best practice for journals to delete copies of it from their editorial systems unless retention is required by local regulations. Journals that retain copies of rejected manuscripts should disclose this practice in their Information for Authors.

When a manuscript is published, journals should keep copies of the original submission, reviews, revisions, and correspondence for at least three years and possibly in perpetuity, depending on local regulations, to help answer future questions about the work should they arise.

Editors should not publish or publicize peer reviewers' comments without permission of the reviewer and author. If journal policy is to blind authors to reviewer identity and comments are not signed, that identity must not be revealed to the author or anyone else without the reviewers' expressed written permission.

Confidentiality may have to be breached if dishonesty or fraud is alleged, but editors should notify authors or reviewers if they intend to do so and confidentiality must otherwise be honored.

b. Timeliness

Editors should do all they can to ensure timely processing of manuscripts with the resources available to them. If editors intend to publish a manuscript, they should attempt to do so in a timely manner and any planned delays should be negotiated with the authors. If a journal has no intention of proceeding with a manuscript, editors should endeavor to reject the manuscript as soon as possible to allow authors to submit to a different journal.

c. Peer Review

Peer review is the critical assessment of manuscripts submitted to journals by experts who are usually not part of the editorial staff. Because unbiased, independent, critical assessment is an intrinsic part of all scholarly work, including scientific research, peer review is an important extension of the scientific process.

The actual value of peer review is widely debated, but the process facilitates a fair hearing for a manuscript among members of the scientific community. More practically, it helps editors decide which manuscripts are suitable for their journals. Peer review often helps authors and editors improve the quality of reporting.

It is the responsibility of the journal to ensure that systems are in place for selection of appropriate reviewers. It is the responsibility of the editor to ensure that reviewers have access to all materials that may be relevant to the evaluation of the manuscript, including supplementary material for e-only publication, and to ensure that reviewer comments are properly assessed and interpreted in the context of their declared relationships and activities.

A peer-reviewed journal is under no obligation to send submitted manuscripts for review, and under no obligation to follow reviewer recommendations, favorable or negative. The editor of a journal is ultimately responsible for the selection of all its content, and editorial decisions may be informed by issues unrelated to the quality of a manuscript, such as suitability for the journal. An editor can reject any article at any time before publication, including after acceptance if concerns arise about the integrity of the work.

Journals may differ in the number and kinds of manuscripts they send for review, the number and types of reviewers they seek for each manuscript, whether the review process is open or blinded, and other aspects of the review process. For this reason and as a service to authors, journals should publish a description of their peer-review process.

Journals should notify reviewers of the ultimate decision to accept or reject a paper, and should acknowledge the contribution of peer reviewers to their journal. Editors are encouraged to share reviewers' comments with co-reviewers of the same paper, so reviewers can learn from each other in the review process.

As part of peer review, editors are encouraged to review research protocols, plans for statistical analysis if separate from the protocol, and/or contracts associated with project-specific studies. Editors should encourage authors

to make such documents publicly available at the time of or after publication, before accepting such studies for publication. Some journals may require public posting of these documents as a condition of acceptance for publication.

Journal requirements for independent data analysis and for public data availability are in flux at the time of this revision, reflecting evolving views of the importance of data availability for pre- and post-publication peer review. Some journal editors currently request a statistical analysis of trial data by an independent biostatistician before accepting studies for publication. Others ask authors to say whether the study data are available to third parties to view and/or use/reanalyze, while still others encourage or require authors to share their data with others for review or reanalysis. Each journal should establish and publish their specific requirements for data analysis and post in a place that potential authors can easily access.

Some people believe that true scientific peer review begins only on the date a paper is published. In that spirit, medical journals should have a mechanism for readers to submit comments, questions, or criticisms about published articles, and authors have a responsibility to respond appropriately and cooperate with any requests from the journal for data or additional information should questions about the paper arise after publication (see Section III).

ICMJE believes investigators have a duty to maintain the primary data and analytic procedures underpinning the published results for at least 10 years. The ICMJE encourages the preservation of these data in a data repository to ensure their longer-term availability.

d. Integrity

Editorial decisions should be based on the relevance of a manuscript to the journal and on the manuscript's originality, quality, and contribution to evidence about important questions. Those decisions should not be influenced by commercial interests, personal relationships or agendas, or findings that are negative or that credibly challenge accepted wisdom. In addition, authors should submit for publication or otherwise make publicly available, and editors should not exclude from consideration for publication, studies with findings that are not statistically significant or that have inconclusive findings. Such studies may provide evidence that, combined with that from other studies through meta-analysis, might still help answer important questions, and a public record of such negative or inconclusive findings may prevent unwarranted replication of effort or otherwise be valuable for other researchers considering similar work.

Journals should clearly state their appeals process and should have a system for responding to appeals and complaints.

e. Diversity and Inclusion

To improve academic culture, editors should seek to engage a broad and diverse array of authors, reviewers, editorial staff, editorial board members, and readers.

f. Journal Metrics

The journal impact factor is widely misused as a proxy for research and journal quality and as a measure of the importance of specific research projects or the merits of individual researchers, including their suitability for hiring, promotion, tenure, prizes, or research funding. ICMJE recommends that journals reduce the emphasis on impact factor as a single measure, but rather provide a range of article and journal metrics relevant to their readers and authors.

3. Peer Reviewers

Manuscripts submitted to journals are privileged communications that are authors' private, confidential property, and authors may be harmed by premature disclosure of any or all of a manuscript's details.

Reviewers therefore should keep manuscripts and the information they contain strictly confidential. Reviewers must not publicly discuss authors' work and must not appropriate authors' ideas before the manuscript is published. Reviewers must not retain the manuscript for their personal use and should destroy copies of manuscripts after submitting their reviews.

Reviewers who seek assistance from a trainee or colleague in the performance of a review should acknowledge these individuals' contributions in the written comments submitted to the editor. These individuals must maintain the confidentiality of the manuscript as outlined above.

Reviewers are expected to respond promptly to requests to review and to submit reviews within the time agreed. Reviewers' comments should be constructive, honest, and polite.

Reviewers should declare their relationships and activities that might bias their evaluation of a manuscript and recuse themselves from the peer-review process if a conflict exists.

D. Journal Owners and Editorial Freedom

1. Journal Owners

Owners and editors of medical journals share a common purpose, but they have different responsibilities, and sometimes those differences lead to conflicts.

It is the responsibility of medical journal owners to appoint and dismiss editors. Owners should provide editors at the time of their appointment with a contract that clearly states their rights and duties, authority, the general terms of their appointment, and mechanisms for resolving conflict. The editor's performance may be assessed using mutually agreed-upon measures, including but not necessarily limited to readership, manuscript submissions and handling times, and various journal metrics.

Owners should only dismiss editors for substantial reasons, such as scientific misconduct, disagreement with the long-term editorial direction of the journal, inadequate performance by agreed-upon performance metrics, or inappropriate behavior that is incompatible with a position of trust.

Appointments and dismissals should be based on evaluations by a panel of independent experts, rather than by a small number of executives of the owning organization. This is especially necessary in the case of dismissals because of the high value society places on freedom of speech within science and because it is often the responsibility of editors to challenge the status quo in ways that may conflict with the interests of the journal's owners.

A medical journal should explicitly state its governance and relationship to a journal owner (e.g., a sponsoring society).

2. Editorial Freedom

The ICMJE adopts the World Association of Medical Editors' definition of editorial freedom (http://wame.org/editorial-independence), which holds that editors-in-chief have full authority over the entire editorial content of their journal and the timing of publication of that content. Journal owners should not interfere in the evaluation, selection, scheduling, or editing of individual articles either directly or by creating an environment that strongly influences decisions. Editors should base editorial decisions on the validity of the work and its importance to the journal's readers, not on the commercial implications for the journal, and editors should be free to express critical but responsible views about all aspects of medicine without fear of retribution, even if these views conflict with the commercial goals of the publisher.

Editors-in-chief should also have the final say in decisions about which advertisements or sponsored content, including supplements, the journal will and will not carry, and they should have final say in use of the journal brand and in overall policy regarding commercial use of journal content.

Journals are encouraged to establish an independent and diverse editorial advisory board to help the editor establish and maintain editorial policy. To support editorial decisions and potentially controversial expressions of opinion, owners should ensure that appropriate insurance is obtained in the event of legal action against the editors, and should ensure that legal advice is available when necessary. If legal problems arise, the editor should inform their legal adviser and their owner and/or publisher as soon as possible. Editors should defend the confidentiality of authors and peer-reviewers (names and reviewer comments) in accordance with ICMJE policy (see Section II C.2.a). Editors should take all reasonable steps to check the facts in journal commentary, including that in news sections and social media postings, and should ensure that staff working for the journal adhere to best journalistic practices including contemporaneous note-taking and seeking a response from all parties when possible before publication. Such practices in support of truth and public interest may be particularly relevant in defense against legal allegations of libel.

To secure editorial freedom in practice, the editor should have direct access to the highest level of ownership, not to a delegated manager or administrative officer.

Editors and editors' organizations are obliged to support the concept of editorial freedom and to draw major transgressions of such freedom to the attention of the international medical, academic, and lay communities.

E. Protection of Research Participants

All investigators should ensure that the planning conduct and reporting of human research are in accordance with the Helsinki Declaration as revised in 2013 (www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). All authors should seek approval to conduct research from an independent local, regional, or national review body (e.g., ethics committee, institutional review board). If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach and demonstrate that the local, regional, or national review body explicitly approved the doubtful aspects of the study. Approval by a responsible review body does not preclude editors from forming their own judgment whether the conduct of the research was appropriate.

Patients have a right to privacy that should not be violated without informed consent. Identifying information, including names, initials, or hospital numbers, should not be published in written descriptions, photographs, or pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives written informed consent for publication. Informed consent for this purpose requires that an identifiable patient be shown the manuscript to be published. Authors should disclose to these patients whether any potential identifiable material might be available via the Internet as well as in print after publication. Patient consent should be written and archived with the journal, the authors, or both, as dictated by local regulations or laws. Applicable laws vary from locale to locale, and journals should establish their own policies with legal guidance. Since a journal that archives the consent will be aware of patient identity, some journals may decide that patient confidentiality is better guarded by having the author archive the consent and instead providing the journal with a written statement that attests that they have received and archived written patient consent.

Nonessential identifying details should be omitted. Informed consent should be obtained if there is any doubt that anonymity can be maintained. For example, masking the eye region in photographs of patients is inadequate

protection of anonymity. If identifying characteristics are de-identified, authors should provide assurance, and editors should so note, that such changes do not distort scientific meaning.

The requirement for informed consent should be included in the journal's instructions for authors. When informed consent has been obtained, it should be indicated in the published article.

When reporting experiments on animals, authors should indicate whether institutional and national standards for the care and use of laboratory animals were followed. Further guidance on animal research ethics is available from the International Association of Veterinary Editors' Consensus Author Guidelines on Animal Ethics and Welfare (http://www.veteditors.org/consensus-author-guidelines-on-animal-ethics-and-welfare-for-editors).

III. Publishing and Editorial Issues Related to Publication in Medical Journals

A. Corrections, Retractions, Republications, and Version Control

Honest errors are a part of science and publishing and require publication of a correction when they are detected. Corrections are needed for errors of fact. Matters of debate are best handled as letters to the editor, as print or electronic correspondence, or as posts in a journal-sponsored online forum. Updates of previous publications (e.g., an updated systematic review or clinical guideline) are considered a new publication rather than a version of a previously published article.

If a correction is needed, journals should follow these minimum standards:

- The journal should publish a correction notice as soon as possible detailing changes from and citing the original publication; the correction should be on an electronic or numbered print page that is included in an electronic or a print Table of Contents to ensure proper indexing.
- The journal should also post a new article version with details of the changes from the original version and the date(s) on which the changes were made.
- The journal should archive all prior versions of the article. This archive can be either directly accessible to readers or can be made available to the reader on request.
- Previous electronic versions should prominently note that there are more recent versions of the article.
- The citation should be to the most recent version.

Pervasive errors can result from a coding problem or a miscalculation and may result in extensive inaccuracies throughout an article. If such errors do not change the direction or significance of the results, interpretations, and conclusions of the article, a correction should be published that follows the minimum standards noted above.

Errors serious enough to invalidate a paper's results and conclusions may require retraction. However, retraction with republication (also referred to as "replacement") can be considered in cases where honest error (e.g., a misclassification or miscalculation) leads to a major change in the direction or significance of the results, interpretations, and conclusions. If the error is judged to be unintentional, the underlying science appears valid, and the changed version of the paper survives further review and editorial scrutiny, then retraction with republication of the changed paper, with an explanation, allows full correction of the scientific literature. In such cases, it is helpful to show the extent of the changes in supplementary material or in an appendix, for complete transparency.

B. Scientific Misconduct, Expressions of Concern, and Retraction

Scientific misconduct in research and non-research publications includes but is not necessarily limited to data fabrication; data falsification, including deceptive manipulation of images; purposeful failure to disclose relationships and activities; and plagiarism. Some people consider failure to publish the results of clinical trials and other human studies a form of scientific misconduct. While each of these practices is problematic, they are not equivalent. Each situation requires individual assessment by relevant stakeholders. When scientific misconduct is alleged, or concerns are otherwise raised about the conduct or integrity of work described in submitted or published papers, the editor should initiate appropriate procedures detailed by such committees as the Committee on Publication Ethics (COPE) (publicationethics.org/resources/flowcharts), consider informing the institutions and funders, and may choose to publish an expression of concern pending the outcomes of those procedures. If the procedures involve an investigation at the authors' institution, the editor should seek to discover the outcome of that investigation; notify readers of the outcome if appropriate; and if the investigation proves scientific misconduct, publish a retraction of the article. There may be circumstances in which no misconduct is proven, but an exchange of letters to the editor could be published to highlight matters of debate to readers.

Expressions of concern and retractions should not simply be a letter to the editor. Rather, they should be prominently labelled, appear on an electronic or numbered print page that is included in an electronic or a print Table of Contents to ensure proper indexing, and include in their heading the title of the original article. Online, the retraction and original article should be linked in both directions and the retracted article should be clearly labelled as retracted in all its forms (abstract, full text, PDF). Ideally, the authors of the retraction should be the same as those of the article, but if they are unwilling or unable the editor may under certain circumstances accept retractions by other responsible persons, or the editor may be the sole author of the retraction or expression of concern. The text of the retraction should explain why the article is being retracted and include a complete citation reference to that article.

Retracted articles should remain in the public domain and be clearly labelled as retracted.

The validity of previous work by the author of a fraudulent paper cannot be assumed. Editors may ask the author's institution to assure them of the validity of other work published in their journals, or they may retract it. If this is not done, editors may choose to publish an announcement expressing concern that the validity of previously published work is uncertain.

The integrity of research may also be compromised by inappropriate methodology that could lead to retraction.

See COPE flowcharts for further guidance on retractions and expressions of concern. See Section IV.g.i. for guidance about avoiding referencing retracted articles.

C. Copyright

Journals should make clear the type of copyright under which work will be published, and if the journal retains copyright, should detail the journal's position on the transfer of copyright for all types of content, including audio, video, protocols, and data sets. Medical journals may ask authors to transfer copyright to the journal. Some journals require transfer of a publication license. Some journals do not require transfer of copyright and rely on such vehicles as Creative Commons licenses. The copyright status of articles in a given journal can vary: Some content cannot be copyrighted (e.g., articles written by employees of some governments in the course of their work). Editors may waive copyright on other content, and some content may be protected under other agreements.

D. Overlapping Publications

1. Duplicate Submission

Authors should not submit the same manuscript, in the same or different languages, simultaneously to more than one journal. The rationale for this standard is the potential for disagreement when two (or more) journals claim the right to publish a manuscript that has been submitted simultaneously to more than one journal, and the possibility that two or more journals will unknowingly and unnecessarily undertake the work of peer review, edit the same manuscript, and publish the same article.

2. Duplicate and Prior Publication

Duplicate publication is publication of a paper that overlaps substantially with one already published, without clear, visible reference to the previous publication. Prior publication may include release of information in the public domain.

Readers of medical journals deserve to be able to trust that what they are reading is original unless there is a clear statement that the author and editor are intentionally republishing an article (which might be considered for historic or landmark papers, for example). The bases of this position are international copyright laws, ethical conduct, and cost-effective use of resources. Duplicate publication of original research is particularly problematic because it can result in inadvertent double-counting of data or inappropriate weighting of the results of a single study, which distorts the available evidence.

When authors submit a manuscript reporting work that has already been reported in large part in a published article or is contained in or closely related to another paper that has been submitted or accepted for publication elsewhere, the letter of submission should clearly say so and the authors should provide copies of the related material to help the editor decide how to handle the submission. See also Section IV.B.

This recommendation does not prevent a journal from considering a complete report that follows publication of a preliminary report, such as a letter to the editor, a preprint, or an abstract or poster displayed at a scientific meeting. It also does not prevent journals from considering a paper that has been presented at a scientific meeting but was not published in full, or that is being considered for publication in proceedings or similar format. Press reports of scheduled meetings are not usually regarded as breaches of this rule, but they may be if additional data tables or figures enrich such reports. Authors should also consider how dissemination of their findings outside of scientific presentations at meetings may diminish the priority journal editors assign to their work.

Authors who choose to post their work on a preprint server should choose one that clearly identifies preprints as not peer-reviewed work and includes disclosures of authors' relationships and activities. It is the author's responsibility to inform a journal if the work has been previously posted on a preprint server. In addition, it is the author's (and not the journal editors') responsibility to ensure that preprints are amended to point readers to subsequent versions, including the final published article.

In the event of a public health emergency (as defined by public health officials), information with immediate implications for public health should be disseminated without concern that this will preclude subsequent consideration for publication in a journal. We encourage editors to give priority to authors who have made crucial data publicly available (e.g., in a gene bank) without delay.

Sharing with public media, government agencies, or manufacturers the scientific information described in a paper or a letter to the editor that has been accepted but not yet published violates the policies of many journals. Such reporting may be warranted when the paper or letter describes major therapeutic advances; reportable diseases; or public health hazards, such as serious adverse effects of drugs, vaccines, other biological products, medical devices. This reporting, whether in print or online, should not jeopardize publication, but should be discussed with and agreed upon by the editor in advance when possible.

The ICMJE will not consider as prior publication the posting of trial results in any registry that meets the criteria noted in Section III.L. if results are limited to a brief (500

word) structured abstract or tables (to include participants enrolled, key outcomes, and adverse events). The ICMJE encourages authors to include a statement with the registration that indicates that the results have not yet been published in a peer-reviewed journal, and to update the results registry with the full journal citation when the results are published.

Editors of different journals may together decide to simultaneously or jointly publish an article if they believe that doing so would be in the best interest of public health. However, the National Library of Medicine (NLM) indexes all such simultaneously published joint publications separately, so editors should include a statement making the simultaneous publication clear to readers.

Authors who attempt duplicate publication without such notification should expect at least prompt rejection of the submitted manuscript. If the editor was not aware of the violations and the article has already been published, then the article might warrant retraction with or without the author's explanation or approval.

See COPE flowcharts for further guidance on handling duplicate publication.

3. Acceptable Secondary Publication

Secondary publication of material published in other journals or online may be justifiable and beneficial, especially when intended to disseminate important information to the widest possible audience (e.g., guidelines produced by government agencies and professional organizations in the same or a different language). Secondary publication for various other reasons may also be justifiable provided the following conditions are met:

1. The authors have received approval from the editors of both journals (the editor concerned with secondary publication must have access to the primary version).
2. The priority of the primary publication is respected by a publication interval negotiated by both editors with the authors.
3. The paper for secondary publication is intended for a different group of readers; an abbreviated version could be sufficient.
4. The secondary version faithfully reflects the authors, data, and interpretations of the primary version.
5. The secondary version informs readers, peers, and documenting agencies that the paper has been published in whole or in part elsewhere—for example, with a note that might read, "This article is based on a study first reported in the [journal title, with full reference]"—and the secondary version cites the primary reference.
6. The title of the secondary publication should indicate that it is a secondary publication (complete or abridged republication or translation) of a primary publication. Of note, the NLM does not consider translations to be "republications" and does not cite or index them when the original article was published in a journal that is indexed in MEDLINE.

When the same journal simultaneously publishes an article in multiple languages, the MEDLINE citation will note the multiple languages (e.g., Angelo M. Journal networking in nursing: a challenge to be shared. Rev Esc Enferm USP. 2011 Dec 45[6]:1281-2,1279-80,1283-4. Article in English, Portuguese, and Spanish. No abstract available. PMID 22241182).

4. Manuscripts Based on the Same Database

If editors receive manuscripts from separate research groups or from the same group analyzing the same data set (e.g., from a public database, or systematic reviews or meta-analyses of the same evidence), the manuscripts should be considered independently because they may differ in their analytic methods, conclusions, or both. If the data interpretation and conclusions are similar, it may be reasonable although not mandatory for editors to give preference to the manuscript submitted first. Editors might consider publishing more than one manuscript that overlap in this way because different analytical approaches may be complementary and equally valid, but manuscripts based upon the same dataset should add substantially to each other to warrant consideration for publication as separate papers, with appropriate citation of previous publications from the same dataset to allow for transparency.

Secondary analyses of clinical trial data should cite any primary publication, clearly state that it contains secondary analyses/results, and use the same identifying trial registration number as the primary trial and unique, persistent dataset identifier.

Sometimes for large trials it is planned from the beginning to produce numerous separate publications regarding separate research questions but using the same original participant sample. In this case authors may use the original single trial registration number, if all the outcome parameters were defined in the original registration. If the authors registered several substudies as separate entries in, for example, clinicaltrials.gov, then the unique trial identifier should be given for the study in question, The main issue is transparency, so no matter what model is used it should be obvious for the reader.

E. Correspondence

Medical journals should provide readers with a mechanism for submitting comments, questions, or criticisms about published articles, usually but not necessarily always through a correspondence section or online forum. The authors of articles discussed in correspondence or an online forum have a responsibility to respond to substantial criticisms of their work using those same mechanisms and should be asked by editors to respond. Authors of correspondence should be asked to declare any competing relationships or activities.

Correspondence may be edited for length, grammatical correctness, and journal style. Alternatively, editors may choose to make available to readers unedited correspondence, for example, via an online commenting system. Such commenting is not indexed in Medline unless it is subsequently published on a numbered electronic or print page. However the journal handles correspondence, it should make known its practice. In all instances, editors must make an effort to screen discourteous, inaccurate, or libellous comments.

Responsible debate, critique, and disagreement are important features of science, and journal editors should encourage such discourse ideally within their own journals about the material they have published. Editors, however, have the prerogative to reject correspondence that is irrelevant, uninteresting, or lacking cogency, but they also have a responsibility to allow a range of opinions to be expressed and to promote debate.

In the interests of fairness and to keep correspondence within manageable proportions, journals may want to set time limits for responding to published material and for debate on a given topic.

F. Fees

Journals should be transparent about their types of revenue streams. Any fees or charges that are required for manuscript processing and/or publishing materials in the journal shall be clearly stated in a place that is easy for potential authors to find prior to submitting their manuscripts for review or explained to authors before they begin preparing their manuscript for submission (http://publicationethics.org/files/u7140/Principles_of_Transparency_and_Best_Practice_in_Scholarly_Publishing.pdf).

G. Supplements, Theme Issues, and Special Series

Supplements are collections of papers that deal with related issues or topics, are published as a separate issue of the journal or as part of a regular issue, and may be funded by sources other than the journal's publisher. Because funding sources can bias the content of supplements through the choice of topics and viewpoints, journals should adopt the following principles, which also apply to theme issues or special series that have external funding and/or guest editors:

1. The journal editor must be given and must take full responsibility for the policies, practices, and content of supplements, including complete control of the decision to select authors, peer reviewers, and content for the supplement. Editing by the funding organization should not be permitted.

2. The journal editor has the right to appoint one or more external editors of the supplement and must take responsibility for the work of those editors.

3. The journal editor must retain the authority to send supplement manuscripts for external peer review and to reject manuscripts submitted for the supplement with or without external review. These conditions should be made known to authors and any external editors of the supplement before beginning editorial work on it.

4. The source of the idea for the supplement, sources of funding for the supplement's research and publication, and products of the funding source related to content considered in the supplement should be clearly stated in the introductory material.

5. Advertising in supplements should follow the same policies as those of the primary journal.

6. Journal editors must enable readers to distinguish readily between ordinary editorial pages and supplement pages.

7. Journal and supplement editors must not accept personal favors or direct remuneration from sponsors of supplements.

8. Secondary publication in supplements (republication of papers published elsewhere) should be clearly identified by the citation of the original paper and by the title.

9. The same principles of authorship and disclosure of relationships and activities discussed elsewhere in this document should be applied to supplements.

H. Sponsorship or Partnership

Various entities may seek interactions with journals or editors in the form of sponsorships, partnerships, meetings, or other types of activities. To preserve editorial independence, these interactions should be governed by the same principles outlined above for Supplements, Theme Issues, and Special Series (Section III.G).

I. Electronic Publishing

Most medical journals are now published in electronic as well as print versions, and some are published only in electronic form. Principles of print and electronic publishing are identical, and the recommendations of this document apply equally to both. However, electronic publishing provides opportunities for versioning and raises issues about link stability and content preservation that are addressed here.

Recommendations for corrections and versioning are detailed in Section III.A.

Electronic publishing allows linking to sites and resources beyond journals over which journal editors have no editorial control. For this reason, and because links to external sites could be perceived as implying endorsement of those sites, journals should be cautious about external linking. When a journal does link to an external site, it should state that it does not endorse or take responsibility or liability for any content, advertising, products, or other materials on the linked sites, and does not take responsibility for the sites' availability.

Permanent preservation of journal articles on a journal's website, or in an independent archive or a credible repository, is essential for the historical record. Removing an article from a journal's website in its entirety is almost never justified as copies of the article may have been downloaded even if its online posting was brief. Such archives

should be freely accessible or accessible to archive members. Deposition in multiple archives is encouraged. However, if necessary for legal reasons (e.g., libel action), the URL for the removed article must contain a detailed reason for the removal, and the article must be retained in the journal's internal archive.

Permanent preservation of a journal's total content is the responsibility of the journal publisher, who in the event of journal termination should be certain the journal files are transferred to a responsible third party who can make the content available.

Journal websites should post the date that nonarticle web pages, such as those listing journal staff, editorial board members, and instructions for authors, were last updated.

J. Advertising

Most medical journals carry advertising, which generates income for their publishers, but journals should not be dominated by advertisements, and advertising must not be allowed to influence editorial decisions.

Journals should have formal, explicit, written policies for advertising in both print and electronic versions. Best practice prohibits selling advertisements intended to be juxtaposed with editorial content on the same product. Advertisements should be clearly identifiable as advertisements. Editors should have full and final authority for approving print and online advertisements and for enforcing advertising policy.

Journals should not carry advertisements for products proven to be seriously harmful to health. Editors should ensure that existing regulatory or industry standards for advertisements specific to their country are enforced, or develop their own standards. The interests of organizations or agencies should not control classified and other nondisplay advertising, except where required by law. Editors should consider all criticisms of advertisements for publication.

K. Journals and the Media

Journals' interactions with media should balance competing priorities. The general public has a legitimate interest in all journal content and is entitled to important information within a reasonable amount of time, and editors have a responsibility to facilitate that. However media reports of scientific research before it has been peer-reviewed and fully vetted may lead to dissemination of inaccurate or premature conclusions, and doctors in practice need to have research reports available in full detail before they can advise patients about the reports' conclusions.

An embargo system has been established in some countries and by some journals to assist this balance, and to prevent publication of stories in the general media before publication of the original research in the journal. For the media, the embargo creates a "level playing field," which most reporters and writers appreciate since it minimizes the pressure on them to publish stories before competitors when they have not had time to prepare carefully. Consistency in the timing of public release of biomedical information is also important in minimizing economic chaos, since some articles contain information that has potential to influence financial markets. The ICMJE acknowledges criticisms of embargo systems as being self-serving of journals' interests and an impediment to rapid dissemination of scientific information, but believe the benefits of the systems outweigh their harms.

The following principles apply equally to print and electronic publishing and may be useful to editors as they seek to establish policies on interactions with the media:

- Editors can foster the orderly transmission of medical information from researchers, through peer-reviewed journals, to the public. This can be accomplished by an agreement with authors that they will not publicize their work while their manuscript is under consideration or awaiting publication and an agreement with the media that they will not release stories before publication of the original research in the journal, in return for which the journal will cooperate with them in preparing accurate stories by issuing, for example, a press release.
- Editors need to keep in mind that an embargo system works on the honor system—no formal enforcement or policing mechanism exists. The decision of a significant number of media outlets or biomedical journals not to respect the embargo system would lead to its rapid dissolution.
- Notwithstanding authors' belief in their work, very little medical research has such clear and urgently important clinical implications for the public's health that the news must be released before full publication in a journal. When such exceptional circumstances occur, the appropriate authorities responsible for public health should decide whether to disseminate information to physicians and the media in advance and should be responsible for this decision. If the author and the appropriate authorities wish to have a manuscript considered by a particular journal, the editor should be consulted before any public release. If editors acknowledge the need for immediate release, they should waive their policies limiting prepublication publicity.
- Policies designed to limit prepublication publicity should not apply to accounts in the media of presentations at scientific meetings or to the abstracts from these meetings (see Duplicate Publication). Researchers who present their work at a scientific meeting should feel free to discuss their presentations with reporters but should be discouraged from offering more detail about their study than was presented in the talk, or should consider how giving such detail might diminish the priority journal editors assign to their work (see Duplicate Publication).
- When an article is close to being published, editors or journal staff should help the media prepare accurate reports by providing news releases, answering questions, supplying advance copies of the article, or referring reporters to appropriate experts. This assistance should be con-

tingent on the media's cooperation in timing the release of a story to coincide with publication of the article.

L. Clinical Trials

i. Registration

The ICMJE's clinical trial registration policy is detailed in a series of editorials (see Updates and Editorials [www.icmje.org/news-and-editorials/] and FAQs [www.icmje.org/about-icmje/faqs/]).

Briefly, the ICMJE requires, and recommends that all medical journal editors require, registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication. Editors requesting inclusion of their journal on the ICMJE website list of publications that follow ICMJE guidance [icmje.org/journals.html] should recognize that the listing implies enforcement by the journal of ICMJE's trial registration policy.

ICMJE uses the date trial registration materials were first submitted to a registry as the date of registration. When there is a substantial delay between the submission of registration materials and their posting at the trial registry, editors may inquire about the circumstances that led to the delay.

The ICMJE defines a clinical trial as any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-related intervention and a health outcome. Health-related interventions are those used to modify a biomedical or health-related outcome; examples include drugs, surgical procedures, devices, behavioral treatments, educational programs, dietary interventions, quality improvement interventions, and process-of-care changes. Health outcomes are any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE does not define the timing of first participant enrollment, but best practice dictates registration by the time of first participant consent.

The ICMJE accepts publicly accessible registration in any registry that is a primary register of the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/network/primary/en/index.html) that includes the minimum acceptable 24-item trial registration dataset or in ClinicalTrials.gov, which is a data provider to the WHO ICTRP. The ICMJE endorses these registries because they meet several criteria. They are accessible to the public at no charge, open to all prospective registrants, managed by a not-for-profit organization, have a mechanism to ensure the validity of the registration data, and are electronically searchable. An acceptable registry must include the minimum 24-item trial registration dataset (http://prsinfo.clinicaltrials.gov/trainTrainer/WHO-ICMJE-ClinTrialsgov-Cross-Ref.pdf or www.who.int/ictrp/network/trds/en/index.html) at the time of registration and before enrollment of the first participant. The ICMJE considers inadequate trial registrations missing any of the 24 data fields, those that have fields that contain uninformative information, or registrations that are not made publicly accessible such as phase I trials submitted to the EU-CTR and trials of devices for which the information is placed in a "lock box." In order to comply with ICMJE policy, investigators registering trials of devices at ClinicalTrials.gov must "opt out" of the lock box by electing public posting prior to device approval. Approval to conduct a study from an independent local, regional, or national review body (e.g., ethics committee, institutional review board) does not fulfill the ICMJE requirement for prospective clinical trial registration. Although not a required item, the ICMJE encourages authors to include a statement that indicates that the results have not yet been published in a peer-reviewed journal, and to update the registration with the full journal citation when the results are published.

The purpose of clinical trial registration is to prevent selective publication and selective reporting of research outcomes, to prevent unnecessary duplication of research effort, to help patients and the public know what trials are planned or ongoing into which they might want to enroll, and to help give ethics review boards considering approval of new studies a view of similar work and data relevant to the research they are considering. Retrospective registration, for example at the time of manuscript submission, meets none of these purposes. Those purposes apply also to research with alternative designs, for example observational studies. For that reason, the ICMJE encourages registration of research with non-trial designs, but because the exposure or intervention in non-trial research is not dictated by the researchers, the ICMJE does not require it.

Secondary data analyses of primary (parent) clinical trials should not be registered as separate clinical trials, but instead should reference the trial registration number of the primary trial.

The ICMJE expects authors to ensure that they have met the requirements of their funding and regulatory agencies regarding aggregate clinical trial results reporting in clinical trial registries. It is the authors', and not the journal editors', responsibility to explain any discrepancies between results reported in registries and journal publications. The ICMJE will not consider as prior publication the posting of trial results in any registry that meets the above criteria if results are limited to a brief (500 word) structured abstract or tables (to include trial participants enrolled, baseline characteristics, primary and secondary outcomes, and adverse events).

The ICMJE recommends that journals publish the trial registration number at the end of the abstract. The ICMJE also recommends that, whenever a registration number is available, authors list this number the first time they use a trial acronym to refer either to the trial they are reporting or to other trials that they mention in the manuscript.

Editors may consider whether the circumstances involved in a failure to appropriately register a clinical trial were likely to have been intended to or resulted in biased reporting. Because of the importance of prospective trial registration, if an exception to this policy is made, trials must be registered and the authors should indicate in the publication when registration was completed and why it was delayed. Editors should publish a statement indicating why an exception was allowed. The ICMJE emphasizes that such exceptions should be rare, and that authors failing to prospectively register a trial risk its inadmissibililty to our journals.

ii. Data Sharing

The ICMJE's data sharing statement policy is detailed in an editorial (see Updates and Editorials [www.icmje.org/update.html]).

1. As of 1 July 2018 manuscripts submitted to ICMJE journals that report the results of clinical trials must contain a data sharing statement as described below.

2. Clinical trials that begin enrolling participants on or after 1 January 2019 must include a data sharing plan in the trial's registration. The ICMJE's policy regarding trial registration is explained at www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. If the data sharing plan changes after registration this should be reflected in the statement submitted and published with the manuscript, and updated in the registry record.

Data sharing statements must indicate the following: whether individual deidentified participant data (including data dictionaries) will be shared ("undecided" is not an acceptable answer); what data in particular will be shared; whether additional, related documents will be available (e.g., study protocol, statistical analysis plan, etc.); when the data will become available and for how long; by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Illustrative examples of data sharing statements that would meet these requirements are provided in the **Table**.

Authors of secondary analyses using shared data must attest that their use was in accordance with the terms (if any) agreed to upon their receipt. They must also reference the source of the data using its unique, persistent identifier to provide appropriate credit to those who generated it and allow searching for the studies it has supported. Authors of secondary analyses must explain completely how theirs differ from previous analyses. In addition, those who generate and then share clinical trial data sets deserve substantial credit for their efforts. Those using data collected by others should seek collaboration with those who collected the data. As collaboration will not always be possible, practical, or desired, the efforts of those who generated the data must be recognized.

IV. Manuscript Preparation and Submission

A. Preparing a Manuscript for Submission to a Medical Journal

1. General Principles

The text of articles reporting original research is usually divided into Introduction, Methods, Results, and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles often need subheadings within these sections to further organize their content. Other types of articles, such as meta-analyses, may require different formats, while case reports, narrative reviews, and editorials may have less structured or unstructured formats.

Electronic formats have created opportunities for adding details or sections, layering information, cross-linking, or extracting portions of articles in electronic versions. Supplementary electronic-only material should be submitted and sent for peer review simultaneously with the primary manuscript.

2. Reporting Guidelines

Reporting guidelines have been developed for different study designs; examples include CONSORT (www.consort-statement.org) for randomized trials, STROBE for observational studies (http://strobe-statement.org/), PRISMA for systematic reviews and meta-analyses (http://prisma-statement.org/), and STARD for studies of diagnostic accuracy (http://www.equator-network.org/reporting-guidelines/stard/). Journals are encouraged to ask authors to follow these guidelines because they help authors describe the study in enough detail for it to be evaluated by editors, reviewers, readers, and other researchers evaluating the medical literature. Authors of review manuscripts are encouraged to describe the methods used for locating, selecting, extracting, and synthesizing data; this is mandatory for systematic reviews. Good sources for reporting guidelines are the EQUATOR Network (www.equator-network.org/home/) and the NLM's Research Reporting Guidelines and Initiatives (www.nlm.nih.gov/services/research_report_guide.html).

3. Manuscript Sections

The following are general requirements for reporting within sections of all study designs and manuscript formats.

a. Title Page

General information about an article and its authors is presented on a manuscript title page and usually includes the article title, author information, any disclaimers, sources of support, word count, and sometimes the number of tables and figures.

Article title. The title provides a distilled description of the complete article and should include information that, along with the abstract, will make electronic retrieval of the article sensitive and specific. Reporting

Table. **Examples of Data Sharing Statements That Fulfill These ICMJE Requirements***

	Example 1	Example 2	Example 3	Example 4
Will individual participant data be available (including data dictionaries)?	Yes	Yes	Yes	No
What data in particular will be shared?	All of the individual participant data collected during the trial, after deidentification.	Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).	Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).	Not available
What other documents will be available?	Study Protocol, Statistical Analysis Plan, Informed Consent Form, Clinical Study Report, Analytic Code	Study Protocol, Statistical Analysis Plan, Analytic Code	Study Protocol	Not available
When will data be available (start and end dates)?	Immediately following publication. No end date.	Beginning 3 months and ending 5 years following article publication.	Beginning 9 months and ending 36 months following article publication.	Not applicable
With whom?	Anyone who wishes to access the data.	Researchers who provide a methodologically sound proposal.	Investigators whose proposed use of the data has been approved by an independent review committee (learned intermediary) identified for this purpose.	Not applicable
For what types of analyses?	Any purpose.	To achieve aims in the approved proposal.	For individual participant data meta-analysis.	Not applicable
By what mechanism will data be made available?	Data are available indefinitely at (*Link to be included).*	Proposals should be directed to xxx@yyy. To gain access, data requestors will need to sign a data access agreement. Data are available for 5 years at a third party website (*Link to be included).*	Proposals may be submitted up to 36 months following article publication. After 36 months the data will be available in our University's data warehouse but without investigator support other than deposited metadata. Information regarding submitting proposals and accessing data may be found at (*Link to be provided*).	Not applicable

* These examples are meant to illustrate a range of, but not all, data sharing options.

guidelines recommend and some journals require that information about the study design be a part of the title (particularly important for randomized trials and systematic reviews and meta-analyses). Some journals require a short title, usually no more than 40 characters (including letters and spaces) on the title page or as a separate entry in an electronic submission system. Electronic submission systems may restrict the number of characters in the title.

Author information. Each author's highest academic degrees should be listed, although some journals do not publish these. The name of the department(s) and institution(s) or organizations where the work should be attributed should be specified. Most electronic submission systems require that authors provide full contact information, including land mail and e-mail addresses, but the title page should list the corresponding authors' telephone and fax numbers and e-mail address. ICMJE encourages the listing of authors' Open Researcher and Contributor Identification (ORCID).

Disclaimers. An example of a disclaimer is an author's statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

Source(s) of support. These include grants, equipment, drugs, and/or other support that facilitated conduct of the work described in the article or the writing of the article itself.

Word count. A word count for the paper's text, excluding its abstract, acknowledgments, tables, figure legends, and references, allows editors and reviewers to assess whether the information contained in the paper warrants the paper's length, and whether the submitted manuscript fits within the journal's formats and word

limits. A separate word count for the abstract is useful for the same reason.

Number of figures and tables. Some submission systems require specification of the number of figures and tables before uploading the relevant files. These numbers allow editorial staff and reviewers to confirm that all figures and tables were actually included with the manuscript and, because tables and figures occupy space, to assess if the information provided by the figures and tables warrants the paper's length and if the manuscript fits within the journal's space limits.

Disclosure of relationships and activities. Disclosure information for each author needs to be part of the manuscript; each journal should develop standards with regard to the form the information should take and where it will be posted. The ICMJE has developed a uniform Disclosure Form for use by ICMJE member journals (www.icmje.org/coi_disclosure.pdf), and the ICMJE encourages other journals to adopt it. Despite availability of the form, editors may require disclosure of relationships and activities on the manuscript title page or other Disclosure section in the manuscript to save the work of collecting forms from each author prior to making an editorial decision or to save reviewers and readers the work of reading each author's form.

b. Abstract

Original research, systematic reviews, and meta-analyses require structured abstracts. The abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical methods), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations, note important limitations, and not overinterpret findings. Clinical trial abstracts should include items that the CONSORT group has identified as essential (www.consort-statement.org/resources/downloads/extensions/consort-extension-for-abstracts-2008pdf/). Funding sources should be listed separately after the abstract to facilitate proper display and indexing for search retrieval by MEDLINE.

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to ensure that they accurately reflect the content of the article. Unfortunately, information in abstracts often differs from that in the text. Authors and editors should work in the process of revision and review to ensure that information is consistent in both places. The format required for structured abstracts differs from journal to journal, and some journals use more than one format; authors need to prepare their abstracts in the format specified by the journal they have chosen.

The ICMJE recommends that journals publish the clinical trial registration number at the end of the abstract. The ICMJE also recommends that, when a registration number is available, authors list that number the first time they use a trial acronym to refer to the trial they are reporting or to other trials that they mention in the manuscript. If the data have been deposited in a public repository and/or are being used in a secondary analysis, authors should state at the end of the abstract the unique, persistent data set identifier; repository name; and number.

c. Introduction

Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

d. Methods

The guiding principle of the Methods section should be clarity about how and why a study was done in a particular way. The Methods section should aim to be sufficiently detailed such that others with access to the data would be able to reproduce the results. In general, the section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the methods.

The Methods section should include a statement indicating that the research was approved by an independent local, regional or national review body (e.g., ethics committee, institutional review board). If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach and demonstrate that the local, regional or national review body explicitly approved the doubtful aspects of the study. See Section II.E.

i. Selection and Description of Participants

Clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age, sex, or ethnicity is not always known at the time of study design, researchers should aim for inclusion of representative populations into all study types and at a minimum provide descriptive data for these and other relevant demographic variables.

Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or

cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance. Authors should use neutral, precise, and respectful language to describe study participants and avoid the use of terminology that might stigmatize participants.

ii. Technical Information

Specify the study's main and secondary objectives—usually identified as primary and secondary outcomes. Identify methods, equipment (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. Identify appropriate scientific names and gene names.

iii. Statistics

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as *P* values, which fail to convey important information about effect size and precision of estimates. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

e. Results

Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

Give numeric results not only as derivatives (e.g., percentages) but also as the absolute numbers from which the derivatives were calculated. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample."

Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

f. Discussion

It is useful to begin the discussion by briefly summarizing the main findings, and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your findings in the context of the totality of the relevant evidence. State the limitations of your study, and explore the implications of your findings for future research and for clinical practice or policy. Discuss the influence or association of variables, such as sex and/or gender, on your findings, where appropriate, and the limitations of the data. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted, but label them clearly.

g. References

i. General Considerations

Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Authors should avoid citing articles from predatory or pseudo-journals. Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published

papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

References to papers accepted but not yet published should be designated as "in press" or "forthcoming." Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

Published articles should reference the unique, persistent identifiers of the datasets employed.

Avoid citing a "personal communication" unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, obtain written permission and confirmation of accuracy from the source of a personal communication.

Some but not all journals check the accuracy of all reference citations; thus, citation errors sometimes appear in the published version of articles. To minimize such errors, references should be verified using either an electronic bibliographic source, such as PubMed, or print copies from original sources. Authors are responsible for checking that none of the references cite retracted articles except in the context of referring to the retraction. For articles published in journals indexed in MEDLINE, the ICMJE considers PubMed the authoritative source for information about retractions. Authors can identify retracted articles in MEDLINE by searching PubMed for "Retracted publication [pt]", where the term "pt" in square brackets stands for publication type, or by going directly to the PubMed's list of retracted publications (https://www.ncbi.nlm.nih.gov/pubmed/?term=retracted+publication+[pt]).

References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses.

References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals). Journals vary on whether they ask authors to cite electronic references within parentheses in the text or in numbered references following the text. Authors should consult with the journal to which they plan to submit their work.

ii. Style and Format

References should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals: Sample References (www.nlm.nih.gov/bsd/uniform_requirements.html) webpage and detailed in the NLM's Citing Medicine, 2nd edition (www.ncbi.nlm.nih.gov/books/NBK7256/). These resources are regularly updated as new media develop, and currently include guidance for print documents; unpublished material; audio and visual media; material on CD-ROM, DVD, or disk; and material on the Internet.

h. Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

Prepare tables according to the specific journal's requirements; to avoid errors it is best if tables can be directly imported into the journal's publication software. Number tables consecutively in the order of their first citation in the text and supply a title for each. Titles in tables should be short but self-explanatory, containing information that allows readers to understand the table's content without having to go back to the text. Be sure that each table is cited in the text.

Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes, and use symbols to explain information if needed. Symbols may vary from journal to journal (alphabet letter or such symbols as *, †, ‡, §), so check each journal's instructions for authors for required practice. Identify statistical measures of variations, such as standard deviation and standard error of the mean.

If you use data from another published or unpublished source, obtain permission and acknowledge that source fully.

Additional tables containing backup data too extensive to publish in print may be appropriate for publication in the electronic version of the journal, deposited with an archival service, or made available to readers directly by the authors. An appropriate statement should be added to the text to inform readers that this additional information is available and where it is located. Submit such tables for consideration with the paper so that they will be available to the peer reviewers.

i. Illustrations (Figures)

Digital images of manuscript illustrations should be submitted in a suitable format for print publication. Most submission systems have detailed instructions on the quality of images and check them after manuscript upload. For print submissions, figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints.

For radiological and other clinical and diagnostic images, as well as pictures of pathology specimens or photomicrographs, send high-resolution photographic image files. Before-and-after images should be taken with the

same intensity, direction, and color of light. Since blots are used as primary evidence in many scientific articles, editors may require deposition of the original photographs of blots on the journal's website.

Although some journals redraw figures, many do not. Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends—not on the illustrations themselves.

Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background. Explain the internal scale and identify the method of staining in photomicrographs.

Figures should be numbered consecutively according to the order in which they have been cited in the text. If a figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce it. Permission is required irrespective of authorship or publisher except for documents in the public domain.

In the manuscript, legends for illustrations should be on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

j. Units of Measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal.

Journals vary in the units they use for reporting hematologic, clinical chemistry, and other measurements. Authors must consult the Information for Authors of the particular journal and should report laboratory information in both local and International System of Units (SI).

Editors may request that authors add alternative or non-SI units, since SI units are not universally used. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

k. Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

B. Sending the Manuscript to the Journal

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