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Optimizing the Trial Design for a Comparative Effectiveness Study of Spironolactone versus Oral Antibiotics for Women with Acne: A Delphi Consensus Panel

John S. Barbieri, MD, MBA[1], **David J. Margolis, MD, PhD**[1,2]

[1]Department of Dermatology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, 19104, USA

[2]Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania, Philadelphia, PA, 19104, USA

For women with acne, their acne often persists into adulthood, with over 50% of women reporting acne between 20–29 years of age and over 35% of women reporting acne between 30–39 years of age.[1] While mild acne can usually be managed with topical medications, moderate to severe acne often requires treatment with systemic medications such as oral antibiotics, spironolactone, and isotretinoin.[2] Although oral antibiotics are the most common systemic medication prescribed for women with moderate to severe acne, spironolactone may represent a safe and effective therapeutic alternative that can decrease our reliance on oral antibiotics for the treatment of acne.[3–5] However, while spironolactone use is increasing, oral antibiotics are still prescribed 3 to 5 times more often than spironolactone.[3]

Notably, 4 out of the top 10 research priorities for the treatment of acne identified by a recent James Lind Alliance Priority Setting Partnership are related to developing additional evidence to understand the appropriate use of systemic medications such as oral antibiotics and spironolactone.[6] In addition, comparing the effectiveness of different long-term treatments for acne was identified by the Institute of Medicine as one of the top priorities for comparative effectiveness research.[7] However, there is a lack of comparative effectiveness data on spironolactone versus oral antibiotics for the treatment of acne, suggesting a need for randomized clinical trials to address this evidence gap.

To identify the optimal study design characteristics of a comparative effectiveness trial of spironolactone versus oral antibiotics, we conducted an online modified Delphi technique among a panel of acne experts.[8] The Delphi consisted of three rounds: an initial qualitative round, followed by 2 quantitative rounds. Prior to the first round, participants were provided with a summary of prior acne trial designs for systemic medications. In the first round, participants responded to open-ended questions regarding key aspects of study design (e.g. primary study outcome assessment, antibiotic type and duration of therapy, use of concomitant topical treatments). Based on the results of the qualitative first round, a series of

Corresponding author: John Barbieri, PCAM 7 South Tower, Philadelphia, PA 19104, USA, Phone: 215-662-2737; Fax: 215-349-8839, john.barbieri@pennmedicine.upenn.edu.

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consensus statements were developed and distributed in an iterative approach with two additional quantitative rounds, in which participants rated proposed study design characteristics on a 1 to 6 scale (1: I do not endorse this approach; 6: I think this approach is acceptable). Following each round, participants were provided with statistical feedback on how their responses compared with those of other participants and revised their original answers in light of feedback and discussion. Our prespecified criteria for consensus were at least 80% of participants rating the item a 5 or 6.

A panel of 16 acne experts was invited to participate, with all 16 participating in each round of the Delphi. There was consensus that the study design should involve simple randomization (100%), that doxycycline should be the active comparator versus spironolatcone (100%), that the dose of spironolactone should be 100mg/day (87.5%) and the dose of doxycycline should be 100mg/day (81.3%). There was consensus that the primary endpoint should be assessed at 16 weeks (100%). There was consensus that study subjects should attest to abstinence or some form of contraception (100%) and should not have changed their contraception method within 3 months of randomization (100%). There was not consensus about concomitant topical therapy (Table 1).

Although spironolactone use has been increasing over the past decade, there is a need for prospective randomized trials comparing spironolactone to oral antibiotics for women with acne.[3] In an informal study of 50 dermatology clinicians (45 dermatologists, 5 advanced practice providers), among those who primarily prescribe oral antibiotics for acne, 70% reported that a trial demonstrating non-inferiority to an oral antibiotic and 100% reported that a trial demonstrating superiority to an oral antibiotic would change their management. Given the potential for a non-inferiority comparative effectiveness study of spironolactone versus doxycycline for acne to shift clinical practice paradigms and inform guideline development, there is an opportunity for future randomized trials to address this evidence gap. The results of this Delphi consensus process outline how to design such a trial to maximize its chances for success.

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Table 1.

Delphi Consensus Statements.

Consensus Statement	Rating						
	1	2	3	4	5	6	5 or 6
The study design will involve simple randomization to either spironolactone or the antibiotic comparator with no dose escalation	0.0%	0.0%	0.0%	0.0%	25.0%	75.0%	100.0%
Doxycycline will be the antibiotic comparator in the study	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%	100.0%
The dose of spironolactone will be 100mg/day	0.0%	0.0%	0.0%	12.5%	0.0%	87.5%	87.5%
The dose of doxycycline will be 100mg/day	0.0%	6.3%	0.0%	12.5%	43.8%	37.5%	81.3%
We will assess the primary endpoint at 16 weeks	0.0%	0.0%	0.0%	0.0%	12.5%	87.5%	100.0%
Study subjects will be required to attest to abstinence or some form of contraception, but they will be allowed to continue their current form of contraception when they enter the study.	0.0%	0.0%	0.0%	0.0%	6.3%	93.8%	100.0%
To be eligible for the study, subjects must not have changed their contraception (e.g. started new combined oral contraceptive) within 3 months of study randomization	0.0%	0.0%	0.0%	0.0%	12.5%	87.5%	100.0%
Study subjects should be allowed to continue their topical regimen that they were using prior to randomization	6.3%	6.3%	6.3%	12.5%	31.3%	37.5%	68.8%
Study subjects should not be allowed to use any topical therapies during the study	43.8%	12.5%	0.0%	12.5%	6.3%	25.0%	31.3%

1: I do not endorse this approach; 6: I think this approach is acceptable

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