PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prospective Swiss cohort study of living-kidney donors - Study protocol
AUTHORS	Gilbert T. Thiel, Christa Nolte, Dimitrios Tsinalis

VERSION 1 - REVIEW

REVIEWER	Catherine M Clase Associate Professor of Medicine Nephrology McMaster University Canada
REVIEW RETURNED	17/06/2011

THE STUDY	There are a number of obvious outcomes in this kind of work, and they are implied in the writing, but the main outcomes (likely development of hypertension, developement of abnormal albuminuria, development of proteinuria, death) are not explicitly defined.
REPORTING & ETHICS	*As I understand it, this protocol is established as routine clinical follow up for all donors in Switzerland, not requiring explicit informed consent (covered in the consent to donation-explicitly or implied?) though donors can opt out. This is an excellent example of integrating research into clinical care; could you explain the ethical thinking and whether the protocol was reviewed by research ethics boards? For example, in our (Canadian) legal framework, no consent would be needed for the follow up if you have decided that that is now the standard of care, but we would be required either to obtain individual patient consent for the use of the information to generate new knowledge (ie the research aspect) or to justify to an ethics board the reasons for 'waiver of consent'. What is the legal and ethical framework of this kind of work in Switzerland?
GENERAL COMMENTS	Terrific work, raised my awareness of barriers to live donation in Switzerland, and an excellent response to a complex medico-societal problem. Congratulations on the work so far and a great idea to publish your protocol. Here are some suggestions for the manuscript, * marks those that I thought more important. P3 line 21 could you clarify how a 'missed donor' is defined in these studies? P4, line 61 what are 'probes'; is this the sample tubes? Are they sent at room temperature regular post without having been centrifuged? What effect might this have on the samples? *P6, line 56. There was little consensus around the measurement of urine albumin at the start of the your study, so I can understand the justification for the study specific definitions that you are using. However, for comparability with others and general comprehensibility, it might be better to consider shifting to the consensus framework and nomenclature suggested in: Levey AS et al. Proteinuria as a Surrogate Outcome in CKD: Report of a Scientific Workshop Sponsored by the National Kidney Foundation and the US Food and Drug Administration Am J Kidney Dis 54:205-226. (table 1) You have all the raw data so this should not pose problems, and I think it is completely ethically acceptable in a long-running study

	such as this to change from a priori definitions to more current definitions and terminology during the course of the study, provided the change can be well justified, as in this case it is. P7, line 18 I wouldn't identify macro-albuminuria with proteinuria (ie they are not the same), you have both separate measurements and we don't know which will be the more relevant prognostic indicator in this setting. P8 I am not sure whether you have a specific question about incisional pain but going forward with your next protocol revision it might be worth including. I appreciate that you are trying to evaluate all kinds of pain, but as you correctly point out, back pain is so common and non-specific that it will be hard to evaluate and without a control group hard to assess the contribution of the nephrectomy. P9, line 7. The three new questions could be described in a separate paragraph from the SF* to avoid confusion. Are they answered on a visual scale or in natural language? P9, line 30. Would you consider including information on life insurance, barriers to insurance, and premiums paid, in future revisions? In Canada some of my colleagues have studied this issue and found that donors are theoretically insurable at rates comparable with controls, but it would be interesting to see this information from another jurisdiction and involving actual patients. *More explicit information on the main outcomes of interest in the statistical section would be helpful. Information on the number of potential patients, feasibility, and perhaps a power calculation around the main estimates would strengthen the manuscript. *I picked up information on study dates from the creatinine assay information, but I suggest including this explicitly in the recruitment section of the protocol. Also the number of transplant centres and volumes at transplant centres could be included. *How are you funded and how long do you plan to follow patients? The English language writing, though perfectly unambiguous and clear, is not completely grammatical and idiomatic. I would be happy to fix this as an uncredited volunteer if it would be helpful. Thanks again for the opportunity to review, and very best wishes for your work,

REVIEWER	Bryce Kiberd Dalhousie University
REVIEW RETURNED	20/06/2011

THE STUDY	The study will largely collect surrogate endpoints (proteinuria and blood pressure). They may also have considerable drop out. They should also have a mechanism to collect hard endpoint data such as ESRD and cardiovascular events especially in those that may be lost to follow up. There is no control population. The text needs to be more fluent, precise, concise and less redundant.
RESULTS & CONCLUSIONS	This is a description of a study and not the report of the results.
GENERAL COMMENTS	The paper is a description for a prospective study of live kidney donors in Switzerland. There has been renewed interest in documenting the potential harm of this practice especially since donor evaluations and criteria have changed (for example less restrictive to include patients with hypertension) and the association of GFR and proteinuria with cardiovascular disease has become

	more apparent. The paper is not particularly well written. There is redundancy and issues with fluency. The authors mention that one of the weaknesses of other studies is the 'lost to follow up'. How much better do they expect to be with this effort? They might improve on this by getting permission to link with other health databases to detect cardiovascular hospitalizations and ESRD especially for those lost to follow up. They want country specific data because they are concerned about the applicability to their population. Do they have evidence that ESRD rates are higher in their country to support this concern? Why have they chosen not to use international gender specific cut points for ACR? Will they require repeat testing for positives. The coefficient of variation of a single ACR is very high with 50% of low positive ACRs returning to negative. Do they plan on recommending the treatment of microalbuminuria with ACEi/ARB. The first sentence at the top of page 10 is unclear. Do they assume that all patients who develop microlabuminuria will have hypertension? They should collect self or physician reported events such as stroke, MI, CHF as these are associated with proteinuria and low GFR. Simply collecting surrogate endpoints without hard clinical events will be a great down fall of this effort. Will patients get medication costs covered? Not sure why the physician gets paid if the patient dies (is this for collection of cause of death?). How many patients do they expect to recruit over the next 10 years? How much do they expect to spend? What is the budget? How likely are they to detect harm? What could be detected that they would recommend that live kidney donation be suspended in their country for ethical reasons? They lack a control population to make these judgements This is a noble and likely expensive effort. Their interest to have active intervention is notable. The information collected will be useful.

VERSION 1 – AUTHOR RESPONSE

Point by Point response letter for bmjopen-2011-000202

"Prospective Swiss cohort study of living-kidney donors - Study protocol"

	1st Reviewer's comments Prof. Catherine M Clase	**Our response**
1.1	There are a number of obvious outcomes in this kind of work, and they are implied in the writing, but the main outcomes (likely development of hypertension, developement of abnormal albuminuria, development of proteinuria, death) are not explicitly defined.	We agree with the Reviewer and have defined the main outcomes. The revised paper now reads as follows (page 2, 2nd para.): ***"In particular the study is designed to prospectively quantify the risks to donors after living kidney donation such as the development of hypertension, albuminuria, renal failure and psychological diseases and to assist in the management of individual donors at an early stage if such complications occur."***
1.2	Terrific work, raised my awareness of barriers to live donation in Switzerland, and an excellent response to a complex medico-societal problem. Congratulations on the work so far and a great idea to publish your protocol. Here are some suggestions for the manuscript, * marks those that I thought more important.	Thank you very much. No reply required.
1.3	* As I understand it, this protocol is established as routine clinical follow up for all donors in Switzerland, not requiring explicit informed consent (covered in the consent to donation- explicitly or implied?) though donors can opt out. This is an excellent example of integrating research into clinical care; could you explain the ethical thinking and whether the protocol was reviewed by research ethics boards? For example, in our (Canadian) legal framework, no consent would be needed for the follow up if you have decided that that is now the standard of care, but we would be required either to obtain individual patient consent for the use of the information to generate new knowledge (ie the research aspect) or to justify to an ethics board the	We have specified the legal and ethical issues in the methods part.st The manuscript reads "The protocol now reasons for 'waiver of consent'. What is the legal and ethical framework of this kind of work in Switzerland?

and the questionnaires were approved by the Ethical
Committee of the University Hospital of Basel and the Swiss Academy of Medical Science (SAMW). No informed consent is required as life long follow-up of living donor's health state is required by the Swiss Transplant Law and as long as data are analysed anonymously. However, to assure compliance to the long term follow up protocol, donors were informed about the aims of the protocol and the registry before their donation. In addition, kidney donors have at any time after donation the option to quite their participation by simply ignoring the invitation from SOL-DHR to visit their family physician."

1.4 a	P3 line 21 could you clarify how 'missed donor' is defined in these studies?	We agree that the term "missed donor" is confusing. We have corrected the sentence which reads now: ***"In these studies** the percent of donors **without follow up data** ranged from 21%[2 3] to 31%[4], to 42%[5 6] up to 77%[7]."*
1.5	P4, line 61 what are 'probes'; is this the sample tubes? Are they sent at room temperature regular post without having been centrifuged? What effect might this have on the samples?	Sorry, we did not realize, that the term "probe" can be misunderstood. We meant samples and have exchanged the term "probe" by the term "sample" throughout the manuscript. As required by the laboratory all samples were sent at room temperature. This might have increased potassium levels in the blood samples only, but potassium was not an outcome measure in the study. The manuscript on page 5, 1st para reads now: "*In the lead-up of a follow-up visit, the study centre sends a little parcel to the kidney donor containing the brief information for the donor and the family physician, a health questionnaire, blood and urine tubes and a pre-paid envelope for sending the **samples at room temperature** to the central laboratory (Viollier AG Basel). The donor makes an appointment with his family physician."* *The Viollier laboratory is receiving samples at room temperature from all over Switzerland,- this is the routine, they ask for. The samples organized by SOL-DHR are a tiny fraction out of those arriving at Viollier. At summer time warm temperature will mainly increase potassium concentration in blood and bacterial count in urine. There is no evidence that creatinine concentration in blood and urine, as well as albumin and protein concentration in urine are altered within 24h at room temperature.*

1.6	*P6, line 56. There was little consensus around the measurement of urine albumin at the start of the your study, so I can understand the justification for the study specific definitions that you are using. However, for comparability with others and general comprehensibility, it might be better to consider shifting to the consensus framework and nomenclature suggested in: Levey AS et al. Proteinuria as a Surrogate Outcome in CKD: Report of a Scientific Workshop Sponsored by the National Kidney Foundation and the US Food and Drug Administration Am J Kidney Dis 54:205-226. (table 1). You have all the raw data so this should not pose problems, and I think it is completely ethically acceptable in a long-running study such as this to change from a priori definitions to more current definitions and terminology during the course of the study, provided the change can be well justified, as in this case it is.	We entirely agree that data on albuminuria need to be presented based on the contemporary definition of cut-off points as published by Levey et al. For clarity reasons we will use the term micro-albuminuria which is commonly used in Europe alongside the term "high albumin excretion" used in North America. We have changed the paragraph in the methods part (p 6, last para) accordingly. The manuscript now reads: ***Data on albuminuria will be presented based on cut-off points defined by the report of the scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. The cut-off-point for albumin excretion to be called micro-albuminuria or high albumin excretion is set to > 30 mg albumin / g creatinin corresponding to ≥ 3.3 mg albumin / mmol creatinine. For clarity reasons we will use the term micro-albuminuria which is commonly used in Europe rather than the term "high albumin excretion" used in North America. For the definition of macro-albuminuria or very high albumin excretion at cut-off point of >300 mg albumin / g creatinine corresponding to 33.9 mg albumin / mmol creatinine was used.***
1.7	P7, line 18 I wouldn't identify macro- albuminuria with proteinuria (ie they are not the same), you have both separate measurements and we don't know which will be the more relevant prognostic indicator in this setting.	We agree entirely with this comment. The original sentence "For the definition of macro-albuminuria, which is identical to the term proteinuria…" was deleted.

1.8	P8 I am not sure whether you have a specific question about incisional pain but going forward with your next protocol revision it might be worth including. I appreciate that you are trying to evaluate all kinds of pain, but as you correctly point out, back pain is so common and non-specific that it will be hard to evaluate and without a control group hard to assess the contribution of the nephrectomy.	We consider several forms of pain during the long-term follow-up. The questionnaires discriminate early postoperative pain from pain possibly related to the long term effects after nephrectomy (e.g. increased pain or change in pain characteristics as compared to the state prior to donation). The protocol uses the term "early post-operative pain" rather than "incisional pain" as in addition to the pain in the area of the incision patients with endoscopic nephrectomy sometimes complain also about shoulder pain do to body positioning during surgery. Information on the early pain is collected in the "early complication questionnaire" collected at the time of discharge from hospital (usually a week after nephrectomy) using an analogue visual scale filled out by the donor him- self. We have specified this aspect in the manuscript on page 8, last paragraph which reads now: **Early** postoperative pain, **which reflects pain at the site of incision and sometimes in case of endoscopic nephrectomy additional shoulder pain do to body positioning during surgery,** is assessed using the visual analogue scale. Information on pain possibly related to the long term effects after nephrectomy is collected in the the basic biannual follow up questionnaire. Back-pain is considered only if specified by the donor or his physician as being clearly more intensive than before donation. We have specified this aspect on page 9 in the new paragraph describing the basic biannual follow up questionnaire. The manuscript now reads: ***Back-pain is considered as nephrectomy related only if specified by the donor or his physician as being clearly more intensive than before donation***
1.9	P9, line 7. The three new questions could be described in a separate paragraph from the SF* to avoid confusion. Are they answered on a visual scale or in natural language?	As recommended by the reviewer we have specified the additional questions in a separate paragraph. As in the SF8 questionnaire the additional questions were presented as MCQs. The 2 separate paragraphs on page 9/10 now read: ***The validated SF-8 multiple choice questionnaire was used to calculate the Physical Component Summary (PCS) and the Mental Component Summary (MCS).*** ***The questionnaire was supplemented by the three following multiple choice questions: 1) In comparison to the last year how would you describe your actual health? 2) How has your emotional relation to the kidney recipient changed since donation? 3) Would you donate a kidney again, if you still had two kidneys?. The answers to these questions are analysed separately from the 8 SF-8 questions.***

1.10	P9, line 30. Would you consider including information on life insurance, barriers to insurance, and premiums paid, in future revisions? In Canada some of my colleagues have studied this issue and found that donors are theoretically insurable at rates comparable with controls, but it would be interesting to see this information from another jurisdiction and involving actual patients.	Yes, of course, we regard this as a major aspect of social donor follow-up. This information is collected prospectively since 2002 in the Social status questionnaire. We have detailed this important point on page 10, 2nd para, which reads now: - *Social status questionnaire (since 2002). This instrument has been developed by* ***SOL-DHR*** *and contains* ***multiple choice*** *questions about the actual professional activity, working capacity, efficiency, and physical fitness and two open questions: 1) draw backs because of donation* ***(e.g. financial, insurance, pension fund or professional disadvantages)*** *and 2)* ***donor's suggestion on possible improvement for the*** *SOL-DHR* ***activity*** *(what can SOL-DHR do better for you?)* For the reviewer's personal interest we would like to illustrate here the importance of this specific issue with insurances by 3 examples 1. The Swiss Transplant Law is asking the transplant centres to take out for each individual donor an insurance covering the risk of death and disability occurring in the first year after donation. The premium has to be paid by the recipient's health insurance. In reality, it was highly difficult to find any Swiss insurance company willing to cover such a risk, since the number of documented and published donor outcomes is too small to calculate the risk for the insurance companies. In addition, insurances are only prepared to insure pools of 100'000 or more risk takers which clearly exceeds the small pool of donors searching for insurance. Finally we found a Swiss life insurance company who now covers death and disability with up to 250'000 Swiss France (~200'000 Euro or ~300'000 US Dollars) for a premium of 500 Swiss Francs (~400 Euro or ~590 US-Dollars) to be paid once. However, the insurance company threatens to massively increase the premium as soon as the first case of damage will occur. No kidney donor has so far died in Switzerland due to kidney donation within the first year. 2. We have seen problems, when a donor wants to improve the status his health insurance plan from basic insurance (which is compulsory in Switzerland for all inhabitants) to private insurance (single bed room in hospital, free choice of surgeon or physician). Health insurance companies have refused to offer more than the compulsory basic insurance plan to kidney donors. This is highly unfair, since at the same time as health insurances confront donors with obstacles the recipients' health insurances are most interested in living kidney donation to avoid the costs of chronic hemodialysis they have to pay for the recipient until transplantation. 3. Furthermore we have observed difficulties with occupational pension's funds, when a donor is becoming employed with a new company with a new pension fund. This pension fund may not be willing to offer the donor

the regular conditions, but rather some handicaps (higher monthly rates or lower percent of income to be paid in case of premature incapability to work due to disease or accident). This is very unfair since no evidence exist, that living donors have a higher risk to become unable to work earlier than non-donors[5]. We hope that evidence collected by the SOL-DHR registry will help solving this insurance problem.

1.11	*More explicit information on the main outcomes of interest in the statistical section would be helpful. Information on the number of potential patients, feasibility, and perhaps a power calculation around the main estimates would strengthen the manuscript.	Thank you we agree and revised the paper as follows: (p. 4, 1 paragraph) "**Until the end of 2010 a total of 1332 living kidney donors have been included (Basel n=521, Berne n=119, Geneva n=111, Lausanne n=151, St. Gallen n=79 and Zurich n=360).**" We also revised the statistics section and added a sample size calculation (based on a survival analysis) for the example of hypertension. The revised section reads as follows (p. 12. Last paragraph) " **Statistical Considerations** **Epidemiologic data and patients' descriptives available on continuous scales will be presented with medians, interquartile ranges or means and standard deviations as appropriate. Categorical data will be presented as rates and percentages. Association of individual (independent) variables on the outcome variables will be reported using correlation coefficients. Main outcomes are the occurrence of albuminuria, hypertension and renal insufficiency as specified above. Secondary outcomes are major somatic and social events such as death, cardiovascular disease, stroke and depression collected from the questionnaires. All outcomes are considered to be dichotomous.** **Results from univariate analysis will inform multivariate modelling. Assessment of causal associations will be performed using multivariate models including potential confounders along with the independent variables of interest. Prognostic scores will be built using either multivariate logistic regression analysis or Cox proportional hazard models. Models will be validated in cross samples. Calibration and discrimination of the cross-validated prognostic instruments will be assessed using the Brier Score. Time-Series analysis will be performed using random effects regression models where appropriate.** **Sample Size Calculations** **The analysis is based on the example of hypertension: We assume that 1 additional kidney donor out of 15 (controls) will develop hypertension. We further assume a follow-up after the accrual interval of 10 years. Prior data indicate that the median survival time on the control treatment is 5 years. If the true median survival times on the control and experimental treatments are 5 and 10 years, respectively, we will need to study 29 subjects developing hypertension and 435 control subjects to be able to reject the null hypothesis that the experimental (post surgery) and control (pre-surgery) survival curves are equal with probability (power) 80%. The Type I error probability associated with this test of this null hypothesis is 0.05.** "

1.12	*I picked up information on study dates from the creatinine assay information, but I suggest including this explicitly in the recruitment section of the protocol. Also the number of transplant centres and volumes at transplant centres could be included.	The registry has started to prospectively collect donor data in 1993. As asked by the reviewer we have amended the manuscript with a paragraph on recruitment, the number of transplant centres and the volumes so far. The new paragraph on page 4 reads: **"Donors from all six kidney transplant centres are included in the SOL-DHR which started 1993. Until the end of 2010 a total of 1332 living kidney donors were registered in the ongoing registry (Basel n=521, Berne n=119, Geneva n=111, Lausanne n=151, St. Gallen n=79 and Zurich n=360)."**
1.13	*How are you funded and how long do you plan to follow patients?	We detailed the funding of SOL-DHR in a new paragraph on page 11 which reads: *"**Funding of SOL-DHR** and Reimbursement for follow-up examination* ***The SOL-DHR expenses are funded by the Swiss Foundation for the follow up care of living organ donors (SNO). The SNO is supported by the government, research and industry funds as well as the Swiss Society of Nephrology. The detailed list of sponsors is given at the end of the manuscript. The running costs of SOL-DHR are kept low as organisation and medical activities of SOL-DHR are provided on a volunteer base by GT since 1993 and DT since 2000."*** In addition we have added details on the funding of the life long donor follow-up examination in the existing paragraph on page 11 which reads now: ***"…The Swiss transplant law requires the health insurances of the kidney recipients to cover the bills from the family physicians for biannual donor follow-up as long as the recipient stays alive with an official pay scale. After recipients death the bills are covered by SNO. The bills for the donor follow-up examination are sent to the SOL-DHR headquarter, which forwards the bill to the health insurance of the kidney recipient. The costs for the chemical analysis in blood and urine of donors: is made for free by the Viollier AG Basel since 1993."***
1.14	The English language writing, though perfectly unambiguous and clear, is not completely grammatical and idiomatic. I would be happy to fix this as an uncredited volunteer if it would be helpful.	Thank you very much for your generous offer for improving our writing. In this revision we tried our best to improve it but, obviously, we fully agree that editing of a native speaker would strongly improve our text. We would kindly ask the Editor to advice us how to proceed.
1.15.	Thanks again for the opportunity to review, and very best wishes for your work,	Thank you for the time spent and your stimulating review that greatly improved the manuscript.

	2nd Reviewer's comments Prof. Bryce Kiberd	Author's response
2.1	The study will largely collect surrogate endpoints (proteinuria and blood pressure). They may also have considerable drop out. They should also have a mechanism to collect hard endpoint data such as ESRD and cardiovascular events especially in those that may be lost to follow up. There is no control population. The text needs to be more fluent, precise, concise and less redundant.	This comment addresses several important issues to which we like to respond separately: **1. Surrogate and hard end points:** The study collects as many hard end points as possible. In particular we document ESRD, strokes, cardiovascular events, diabetes or malignancies during the donor follow-up. If we do not receive a response from the donor within 2 months of the scheduled biannual follow-up possible data on donor death and its reason is collected by contacting the recipient, the donor health insurance or the public registries. We have clarified this on page 5 last paragraph and added a new paragraph to the manuscript with detailed information on the biannual follow up examination and questionnaire. The amendment to the manuscript on page 5 reads: ***"If no response from the donor is received within 2 months after the scheduled biannual send out of the follow-up material SOL-DHR initiates a search for the donor and to collect possible data on donor death and its reason by contacting the recipient, the donor's health insurance and the public registries."*** See page 9, 2nd para. **"The basic biannual follow up questionnaire The family physician is requested … to file-out the medical questionnaire including questions about pain and all serious health problems including major events such as stroke, cardiovascular events, diabetes or malignacies since the last examination."** **2. Mechanism to collect hard data endpoints** In additional to the mechanism detailed above a backup mechanism to collect hard end point data especially on ESRD is the compulsory Swiss health insurance system, where insurances always contact SOL-DHR in case of a serious health event of the donor as such costs have to be covered by the recipient's health insurance. **3. risk of drop out** See also response to comment 2.4 Since the study has started in 1993 we have an overall lost to follow up of 14% of donors, which is smaller than the respective figure in any study published so far. However, we feel that this figure should be reported and discussed as an outcome data in the result part of the registry report, rather than in this manuscript detailing the study protocol.

2.1 cont.		**4. Control population** Control populations is an main issue in this cohort study, which has two control groups: For hypertension we use the MONICA-study, with data from a normal Swiss population as control. Primavista this looks like a very sound control. However, we have realised that living donors are a positive selection out of the normal population. Kidney donors are "healthier" than the normal population resulting in underreporting of health risks. The ideal control group would be data of age matched potential donors without donation but lifelong biannual follow-up. This seems not realistic. However, the collected data from a large donor population of any age collected immediately before donation can be used to define the normal outcome of this positively selected donor population. Meanwhile we have data available from 1332 donors so far examined before donation which can be used as age and gender matched control cohort for comparison with the donor population after nephrectomy. There is a strong consensus in our biostatistical advisory expert panel that the large number of healthy donors collected so far provides a much stronger control cohort as reported in any similar study so far. We have specified the control cohort adding a specific paragraph to the manuscript. The paragraph on page 12 now reads: ***" Control population*** ***To control for the risk of developing hypertension the MONIKA-study, with data from a normal Swiss population was used. However, living donors are a positive selection out of the normal population. Kidney donors are "healthier" than the normal population resulting in a potential underreporting of health risks. To directly compare the normal outcome of such a healthy cohorts, pooled data from the SOL-DHR's own healthy donor population taken prior to nephrectomy (n=1332) is used to analyse the outcome of this positively selected donor population after donation."***
		5. English language, fluency and redundancies We would like to refer to our reply 1.14 of Reviewer 1. .
2.2	The paper is a description for a prospective study of live kidney donors in Switzerland. There has been renewed interest in documenting the potential harm of this practice especially since donor evaluations and criteria have changed (for example less restrictive to include patients with hypertension) and the association of GFR and proteinuria with cardiovascular disease has become more apparent.	No response required.

2.3	The paper is not particularly well written. There is redundancy and issues with fluency.	We are sorry for this and would like to refer to our reply 1.14 of Reviewer 1.
2.4	The authors mention that one of the weaknesses of other studies is the 'lost to follow up'. How much better do they expect to be with this effort? They might improve on this by getting permission to link with other health databases to detect cardiovascular hospitalizations and ESRD especially for those lost to follow up.	See also our response 3 to reviewer's comments 2.1. The loss to follow-up or incomplete data sets is a weakness in any long term follow-up study and especially in retrospective designs. To reduce this risk the present study was designed and data collected prospectively. To further reduce the loss to follow-up we have, as suggested by the reviewer, linked the study to the Swiss Health Institution (so called SVK), where 95% of Swiss Health insurances are connected. This is helpful for detecting ESRD (see our response 2 to comment 2.1.)
2.5	They want country specific data because they are concerned about the applicability to their population. Do they have evidence that ESRD rates are higher in their country to support this concern?	We do not have data nor are we seriously concerned that the ESRD rate in our country differs from rates in countries with similar health systems and compulsory health insurances. However, the demand for country specific data originates mostly from legislative agencies and health insurances involved in optimising the legal and insurance framework for living organ donation.
2.6	Why have they chosen not to use international gender specific cut points for ACR? Will they require repeat testing for positives. The coefficient of variation of a single ACR is very high with 50% of low positive ACRs returning to negative.	We entirely agree with the reviewer that results have to be presented as international gender specific cut points for albumin / creatinine ratio. The manuscript has been changed accordingly (see also response to comment 1.6.) We have changed the paragraph in the methods part (p 6, last para) accordingly. The manuscript now reads: ***Data on albuminuria will be presented based on cut-off points defined by the report of the scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration.*** Whenever during a follow-up a laboratory results (creatinine or albumin/creatinine ratio) exceeded the expected range in an individual donor, the sampling and the laboratory analysis is repeated. The manuscript has been amended accordingly on page 6, 3rd paragraph.

		The unclear sentence on page 10 regarding treatment recommendations has be deleted from the manuscript as it is not relevant to the study protocol. However, for the reviewer's interest we would like to answer his questions in this letter: Yes, we recommend ACEI/ARB treatment for the usual case of hypertensive donors developing albuminuria. We do not assume that all patients developing microalbuminuria will have hypertension. In our data set nearly 70% of donors with a urinary albumin/creatinine ratio ≥ 5.0 have hypertension as well. In the group developing rising albuminuria without hypertension and without abnormal urinary sediment, albuminuria is the majority of cases the first sign of glomerular hyperfiltration damage. Low dose ACEI or ARB treatment would the adequate treatment for glomerular protection, which we do indeed recommend. We feel that this information does not belong to the study protocol but needs to be presented and discussed in a separate manuscript reporting the various outcomes of this study.
2.7	Do they plan on recommending the treatment of microalbuminuria with ACEi/ARB. The first sentence at the top of page 10 is unclear. Do they assume that all patients who develop microlabuminuria will have hypertension?	
2.8	They should collect self or physician reported events such as stroke, MI, CHF as these are associated with proteinuria and low GFR. Simply collecting surrogate endpoints without hard clinical events will be a great down fall of this effort.	See also our response 1 to reviewer's comments 2.1. All hard end points such as stroke, MI, CHF and ESRF are collected. This is detailed in the manuscript on page 9, 2nd para, which reads. **"The family physician is requested … to file-out the medical questionnaire including questions about pain and all serious health problems including major events such as stroke, cardiovascular events, diabetes or malignancies since the last examination."**
2.9	Will patients get medication costs covered? Not sure why the physician gets paid if the patient dies (is this for collection of cause of death?).	Yes, all medications required by kidney donors are paid by the donor's own health insurance. All individuals living in Switzerland have a compulsory basic health insurance which pays for all drugs. We have amended the manuscript on page 12, 1st para, which reads: ***"Cost for drugs required by the donor are paid by the compulsory health insurance of the donor independently whether the drug treatment is related to donation or not."*** After death of the patient (recipient) the donors family physician still gets paid for performing the biannual follow-up examinations of the donor. We have clarified this in the manuscript on page 11, which reads: *"After recipient's death the bills **for the donor follow-up** are covered by SNO."* The abbreviation SNO for Swiss Foundation for the follow-up care of living organ donors is defined in the manuscript in the paragraph above.

		Number of donor recruitments (we recruit donors not patients!)
2.10	How many patients do they expect to recruit over the next 10 years? How much do they expect to spend? What is the budget? How likely are they to detect harm? What could be detected that they would recommend that live kidney donation be suspended in their country for ethical reasons? They lack a control population to make these judgements	Please, see also response to reviewer's comment 1.12. Since the start of the prospective study in 1993 until the end of 2010 we have registered 1'332 donors in SOL-DHR. The rate of living kidney donations has increased during the study and is now in the range of 120 kidneys per year. We expect to recruit addition 1'200 kidney donors over the next 10 years reaching a total of more than 2'500 kidney donors. Since January 2008 we follow living liver donors as well. **Budget** Please, see also response to reviewer's comment 1.13. The budget for the next 10 years is 950'000 Swiss Francs (~1 Million US$). The study funding is detailed in a new paragraph on page 11 (Funding of SOL-DHR…) **Likelihood to detect harm after donation** Based on the 18 years of SOL-DHR activity we realise that the likelihood to detect harm after donation is considerable. However, we feel that this important information does not belong to the study protocol but needs to be presented and properly discussed in a separate manuscript reporting the various outcomes of this study. After 18 years of SOL-DHR activity, we cannot imagine any finding which would let us recommend stopping living donation in Switzerland for ethical reason. The goal of this study is not to recommend stopping living donation but to collect the data needed to properly inform potential donors before donation and to assure optimal follow-up care after donation. This is felt as an ethical obligation.
2.11	This is a noble and likely expensive effort. Their interest to have active intervention is notable. The information collected will be useful.	Thank you. We plan to communicate the collected information shortly.

VERSION 2 - REVIEW

REVIEWER	Catherine Clase McMaster University
REVIEW RETURNED	21/07/2011

THE STUDY	As I mentioned before, if it would help I would be happy to try to make the manuscript more grammatical as an uncredited volunteer.

VERSION 2 – AUTHOR RESPONSE

Dr. Clase has worked incredibly well on the text and has improved it a lot. She also made very helpful comments. The revised version is ready to be submitted. We clarified the contributions for this paper and we acknowledge Dr. Clase and me for the support.